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A study on dose response of NIPAM-based dosimeter used in radiotherapy

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Abstract The newly manufactured *N*-isopropylacrylamide (NIPAM) polymer gel is composed of four components, i.e., gelatin, monomer (NIPAM), crosslinker (*N,N'*-methylenebisacrylamide, Bis), and antioxidant (tetrakis hydroxymethyl phosphonium chloride, THPC). In this study, we investigated the effects of gel composition on the dose response of NIPAM polymer gel. A statistical experiment to analyze the contribution of each composition to the linearity and sensitivity of NIPAM gel was performed. Results indicate that the amount of gelatin, NIPAM (15.17%), Bis, and THPC have dominant effects on the sensitivity of the gel, with contributions of 59.73, 15.17, 10.64, and 14.45%, respectively. The amount of gelatin and Bis mainly affected the linearity of the gel, with contributions of 44.70 and 50.99%, respectively. The linearity of most compositions of the gel was greater than 0.99 when $(\%C)/(\%T)$ was lower than 8.0. Optimal $(\%C)/(\%T)$ for higher sensitivity should be in the range of 4−9. The temporal stability experiment showed that the dose response curve attained stability at about 5 h after irradiation and persisted up to 3 months.

Keywords Dose response · NIPAM gel · Monomer · Crosslinker · Tetrakis hydroxymethyl phosphonium chloride

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Introduction

The increasing demand for quality assurance in radiotherapy led to tremendous development in radiation dosimetry in recent years [1]. Previous studies [2–4] have found that the gel dosimeter is one of the best technologies to achieve validation of 3-D dose distribution. Gel dosimeter is advantageous because of its high spatial resolution and precision, especially at high dose gradients. The two main types of gel are the Fricke gel and the polymer gel. The Fricke gel is based on the Fricke chemical reaction after irradiation, in which ferrous ions (Fe^{2+}) are converted to ferric ions (Fe^{3+}). Since ferric ions produce a stronger paramagnetic enhancement of water-proton NMR relaxation rates, the ions can be detected and imaged by nuclear magnetic resonance (NMR) or MR imaging [5, 6]. However, the ions cannot retain a stable spatial dose distribution because ferric ions diffuse rapidly with time, which eventually destroys spatial dose information [7, 8]. One type of polymer gel, the polyacrylamide (PAG) gel, was introduced in 1993 to replace Fricke gel with acrylic monomers [9]. Early studies focused on crosslinking Bis, acrylamide, and poly-acrylamide gel based on radiation-induced polymerization. The formation of acrylic polymer chains addressed the problem of Fricke gels because the long polymer chains are large enough to prevent rapid diffusion

of ions [10]. Maryanski [11] proposed a new type of gel, the BANG-1® (trademark of MGS), which is composed of Bis (*N*,*N*′-methylene-bis-acrylamide) (3%), Acrylamide (3%), nitrogen, gelatin (5%), and de-ionized water (89%) by w/w. Subsequent improvements to BANG-2 [12] and BANG-3 [13] decreased monomer toxicity and increased gel sensitivity.

However, polymerization and crosslinking reactions are inhibited in an oxygen-contaminated polymer gel dosimeter [14]. To avoid oxygen diffusion into the gel, a new antioxidant, tetrakis hydroxymethyl phosphonium chloride (THPC), was proposed to replace ascorbic acid. THPC was found to produce the highest reaction rate and was capable of increasing the dose sensitivity of the gel [15, 16]. In 2005, another normoxic polymer gel was proposed: PAGAT (PAG adds THPC) polymer gel can be manufactured on the bench top under normal atmospheric conditions with the addition of THPC antioxidant [17]. The manufacturing method of the PAGAT polymer gel addressed the requirement for strict hypoxic atmospheric conditions of PAG polymer fabrication, where oxygen acts as an inhibitor of the polymerization process [9, 11, 15, 16].

To eliminate the high toxicity of the monomer, Senden et al. [18] proposed the *N*-isopropyl acrylamide (NIPAM) polymer gel, which is based on a less toxic monomer. The composition of NIPAM polymer gel used in Senden's study was gelatin (5%), NIPAM (3%), Bis (3%), and THPC (10 mM). However, the quantitative contribution of each composition to dose response is not clear. Jirasek et al. [19] asserted that the interaction between THPC and gelatin induces additional crosslinking, which affects the dose response of the gel. Furthermore, the decrease in water upon addition of gelatin causes termination of the polymerization reaction [20]. Chain et al. [21] reported a new cosolvent-free NIPAM polymer gel recipe with increased dose sensitivity, which was capable of maintaining gel stiffness with 3 wt% gelatin and 5 mM THPC. They found that gelatin concentration has a substantial effect on the dose response with optical imaging. However, the quantitative effect of gel compositions on dose response remained unknown. Chang et al. [22] adopted an experimental design to determine the optimal composition of NIPAM polymer gel. Results showed that the optimal gel composition for the dose range 0–15 Gy with linearity of up to 1.0 is as follows: gelatin (5.67%), NIPAM (5%), Bis (2.56%), and THPC (10 mM). The effect of the specified amount of each component on dose response was not mentioned. Koeva et al. [23] proposed a mathematical model for crosslinking copolymerization of NIPAM and Bis to describe the polymerization reaction process in gel dosimeter. Results suggested that further understanding of the chemical reaction involving THPC was required because its influence was not included in the model.

Therefore, the present study conducted statistical experiments to investigate the effects of the amount of each gel component on dose response [24]. In addition, this study try to identified the range of concentration of each gel component that could lead to higher linearity and sensitivity.

Materials and methods

NIPAM polymer gel preparation and irradiation

Gel samples were manufactured following the method described by Senden [18]. First, a 5 wt% gelatin (300 Bloom Type A, Sigma-Aldrich) was added to 89 wt% de-ionized water and stirred for 5 min at room temperature of 22 °C. The gelatin solution was heated to 45 °C by an electric heater until it became clear and transparent. With continuous stirring, 3 wt% Bis (Merck) and 3 wt% NIPAM (97%, Sigma-Aldrich) were poured into the gelatin solution and dissolved; this took about 15 min. Afterwards, 10 mM THPC was added to the solution and continuous stirring was done for 2 min. Finally, gel solutions were transferred into Pyrex screw test vials (16 mm Outer Diameter, 100 mm length, Model No. 9826) and wrapped in aluminum foil to prevent photo-polymerization. Upon completion of the manufacturing process, polymer gels were carefully stored in a room maintained at 22 °C until complete solidification. Each composition was manufactured in triplicate.

Figure 1 shows the flowchart of the gel irradiation process. To avoid oxygen diffusion, irradiation with 6 MV beam from a linear accelerator (Varian 21X Clinac, Varian Ltd., Palo Alto, CA, USA) was performed less than 6 h after gel fabrication. In the center of the short side of a customized 30 × 30 × 4 cm^3 acrylic phantom, a hole with 16-mm diameter was punctured to accommodate the position of Pyrex test vials. The un-irradiated gel vial was placed in the hole in the acrylic phantom to provide adequate build-up and scattering conditions. To secure the precise location, two acrylic sticks 3.5 and 16.5 cm in length, respectively, were placed adjacent to the upper and lower sides of the test tube. The acrylic phantom was placed between two pieces of 3-cm solid water phantoms to ensure that source surface distance was 5 cm.

The setup condition of linear accelerator is as follows: gantry, 0°; field size, 10 × 10 cm^2; and photon energy, 6 MV. To evaluate spatial stability, the lateral profile of dose distribution at the central axis of the gel sample was calibrated using an ion chamber (cavity, 0.147 cc; diameter, 0.6 cm) in the water phantom. Each composition was irradiated at various doses: 0.5, 1, 1.5, 2, 4, 5, 8, 10, 20, 30, 40, and 50 Gy. Experiments were conducted on three batches of gels with preparation times varying from 4.5–312 h to investigate various post-irradiation times.

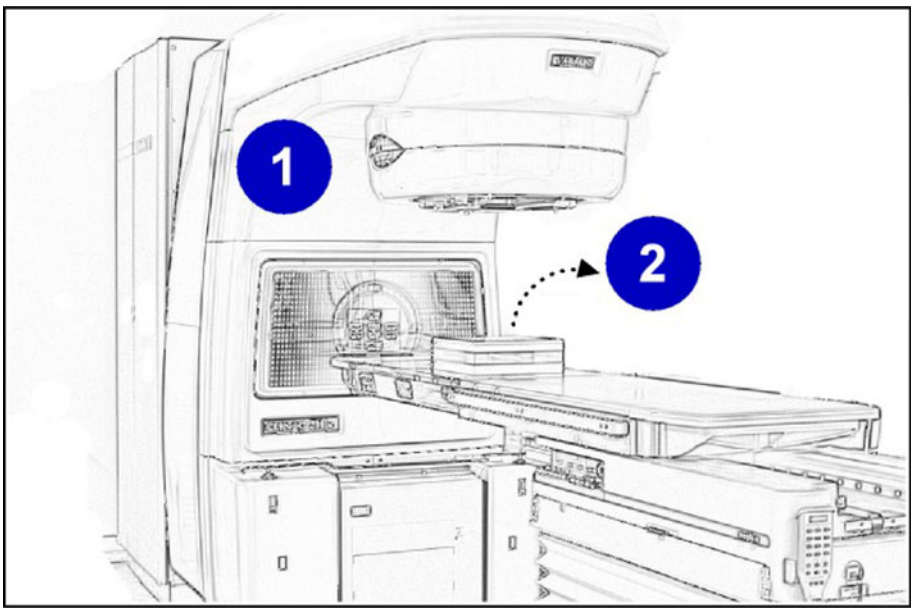

Fig. 1 Experimental setup of the *n*-NIPAM gel irradiation system: (*1*) linear accelerator; (*2*) Phantom

Measurement of attenuation coefficient

An apparatus (CT-s1; Fig. 2) was developed to scan the polymer gel dosimeter. The experimental setup and measurement procedure are also presented in Fig. 2. The laser used in CT-s1 was an NRC Model 127 Helium–Neon laser with 20 mW power and 632.8 nm wavelength. After 140 min of laser warm up, the deviation of output light intensity was less than 1.0%. Room temperature was maintained at 22 ± 1 °C using an air-conditioner. Figure 2 shows that the laser beam was divided into two equal components by a beam splitter. One beam, which passed through an unirradiated gel, was used as reference beam. Light intensity of the reference beam was recorded as initial optical intensity I_0. The unirradiated gel was encapsulated in a Pyrex screw test vial, which was mounted on a stage in a 51 × 75 × 90 mm^3 tank. The tank was filled with vegetable oil with a refractive index similar to that of the Pyrex glass to minimize refraction and reflection at the interface. The other beam, which passed through the irradiated gel, was used as object beam. Light intensity of the object beam was recorded as instantaneous optical intensity I. The irradiated gel was encapsulated in the same type of Pyrex screw test vial and tank as the unirradiated gel. In addition, the Pyrex screw test vial was mounted on a four-axes stage, i.e., three orthogonal linear axes (x, y, z) and a rotational axis (θ), to move the gel to a scanning location and angle. Optical intensity I_0 and I were obtained from the readout of optical power meters. The degree of laser attenuation and irradiation dose of the gel can be represented as attenuation coefficient α, which is defined as

$$\alpha = -\frac{1}{x}\ln\left(\frac{I}{I_0}\right) \tag{1}$$

where x is the diameter of gel, I_0 is the optical intensity of the laser beam passing through the unirradiated sample, and I is the optical intensity of the laser beam penetrating the irradiated sample. The maximum uncertainty of the attenuation coefficient is estimated to be less than 2.97% for all cases using the uncertainty estimation method according to Oldham et al. [25].

Experimental design

In order to differentiate the effects of the amount of each component on the dose response of the NIPAM gel, we conducted adopted the statistical experimental design [24]. In the present case of four controllable factors at three different levels, the standard $L_9(3^4)$ orthogonal array was selected for the experimental design matrix. The four factors were the amount of each component, i.e., gelatin, NIPAM, Bis, and THPC. Table 1 shows the controlled factors and levels. The compositions of the gel had different contributions to the sensitivity and linearity of NIPAM gel at various dose ranges. Experimental results identified and investigated by the statistical software (DESIGN-EXPERT software) were analyzed to find the contribution of each composition. The optical dose–response curve, measured in terms of the attenuation coefficient and absorbed dose for each polymer gel recipe, can be correlated by the following expression:

$$y = \beta x \tag{2}$$

where β is the slope that denotes sensitivity, which is obtained using the formula in Zero-point proportional form.

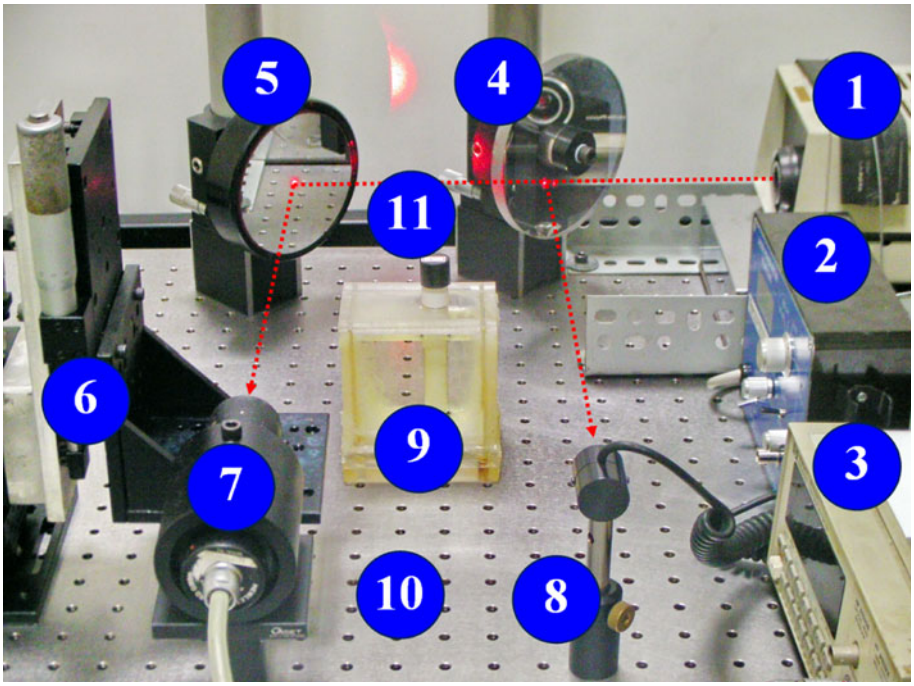

Fig. 2 Schematic diagram of the setup for measuring attenuation coefficient using CT-s1. (*1*) 632.8 nm He–Ne laser; (*2*) optical power meter; (*3*) Multimeter system; (*4*) Beam splitter; (*5*) mirror; (*6*) three-axes stage; (*7*) optical sensor head; (*8*) optical sensor head; (*9*) oil tank; (*10*) optical table; (*11*) optical path

Table 1 Control factors and levels used in the experiment

Coded levels	Gelatin (%)	NIPAM (%)	Bis (%)	THPC (mM)
1	5.5	4	2.5	4.5
2	6	4.5	3	5
3	6.5	5	3.5	5.5

Table 3 Effect estimate for sensitivity

Factor	Gelatin	NIPAM	Bis	THPC
Sum of square	2.624E−05	6.667E−05	4.675E−05	6.35E−05
Percent contribution (%)	59.73	15.17	10.64	14.45

Results and discussion

Statistical analysis of sensitivity and linearity

Linearity and sensitivity data were entered into the design matrix (Table 2) as planned by the statistical software to identify significant variables. The effect estimates and sums of the squares of gel composition in relation to sensitivity and linearity are presented in Tables 3 and 4, respectively. Percent contribution indicates the relative importance of each model term. Gelatin had the dominant effect on the sensitivity of the gel, with a contribution of 59.73%. The other three factors had less contribution to the sensitivity of the gel, i.e. NIPAM with 15.17%, THPC with 14.45%, and Bis with 10.64%, although their effects were still important for gel sensitivity. Table 4 shows that the

Table 2 Linearity and sensitivity of the gels

Run	Gelatin (%)	NIPAM (%)	Bis (%)	THPC (mM)	Sensitivity	Linearity
1	5.5	4	2.5	4.5	0.0279 ± 0.01158	0.990 ± 0.00098
2	5.5	4.5	3	5.0	0.0326 ± 0.01559	0.992 ± 0.00351
3	5.5	5	3.5	5.5	0.0336 ± 0.01250	0.996 ± 0.00692
4	6	4	3	5.5	0.0167 ± 0.00523	0.998 ± 0.00628
5	6	4.5	3.5	4.5	0.0274 ± 0.01351	0.998 ± 0.00283
6	6	5	2.5	5.0	0.0135 ± 0.00030	0.994 ± 0.00080
7	6.5	4	3.5	5.0	0.0159 ± 0.00400	0.997 ± 0.03002
8	6.5	4.5	2.5	5.5	0.0202 ± 0.00571	0.993 ± 0.00213
9	6.5	5	3	4.5	0.0261 ± 0.00938	0.996 ± 0.00397

Table 4 Effect estimate for linearity

Factor	Gelatin	NIPAM	Bis	THPC
Sum of square	2.900E−05	1.197E−06	3.308E−05	1.596E−06
Percent contribution (%)	44.70	1.85	50.99	2.46

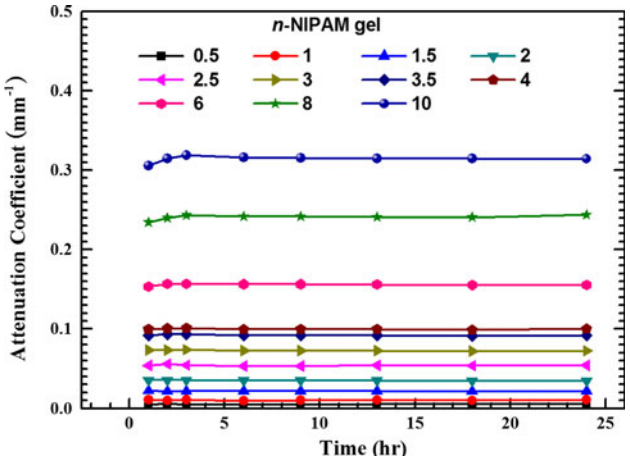

Fig. 3 Temporal stability of *n*-NIPAM gel irradiated with various doses (Gy)

amount of gelatin and Bis were the main contributors to the linearity of the gel, contributing 44.70 and 50.99%, respectively. Amount of NIPAM (1.85%) and THPC (2.46%) had relatively less contribution to the linearity of the gel.

As mentioned in previous studies [20], the polymer gel dosimeter is based on radiation-induced polymerization, which is affected by gelatin. When adding gelatin, the number of OH· radicals is decreased. Since OH· radicals interact with the growing polymer chain and terminate the polymerization reaction the addition of gelatin decreases the likelihood of termination of polymerization. However, the quantitative effect of gelatin to sensitivity has not been identified previously. Bis can react with gelatin to produce a more rigid crosslinking structure, which causes a proportional increase in radiation dose per unit [26].

Previous studies [19] have demonstrated that the addition of THPC increases gelatin coagulation due to decreased monomer mobility in the gel. Furthermore, they have found that a full dose response can be achieved by adding more than 4.5 mM of THPC. Results of the present study are consistent result with those of previous studies.

Temporal stability

Figure 3 shows the variation of attenuation coefficient with various post-irradiation times. Gel samples were irradiated with doses of 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, and 10 Gy. From the range of 1−25 h post-irradiation, NIPAM gel became stable at 5 h post-irradiation, which can reduce environmental interference affecting dose distribution of gel after irradiation. Furthermore, the temporal stability of this optimal *n*-NIPAM gel allows the radiotherapist to reduce waiting time in treatment planning. In addition, comparison of dose response curves of NIPAM polymer gel with post irradiation time of—3, 6, 9, 15, 18, and 24 h and 7 and 40 days—revealed that both sensitivity and linearity of the gel had less than 1% deviation from the mean value. In the present study, all sample gels of attenuation coefficient were measured at 25 h post-irradiation to reduce temporal instability.

The temporal stability of a gel after irradiation indicates clinic applicability. In order to verify the temporal stability of the gel, the deviation of sensitivity and linearity were measured at various times after irradiation. Table 5 shows the worst case, where the deviation of sensitivity was less than 6% at almost 3 months post-irradiation. Three batches of gel samples were measured for replication. In addition, deviation of the linearity of the gel was less than 0.2% at almost 3 months post-irradiation. In general, all gels investigated in the present study showed long-term stability within 2% deviation. According to Senden et al. [18], the chemical reaction persisted until 24 h after irradiation due

Table 5 Temporal stability of NIPAM gel for dose range of 0−10 Gy

Experimental design variables				Sample gel	Date of measurement	Sensitivity 0–10 Gy	Deviation of sensitivity (%)	Linearity 0–10 Gy	Deviation of linearity (%)
Gelatin (%)	NIPAM (%)	Bis (%)	THPC (mM)						
6	5	2.5	5	Batch 1	May/12/2009	0.0138	5.8	0.995	0.1
					Aug/04/2009	0.0130		0.996	
				Batch 2	May/13/2009	0.0135	3.7	0.994	0.2
					Aug/05/2009	0.0130		0.996	
				Batch 3	May/14/2009	0.0132	3.8	0.994	0.0
					Aug/06/2009	0.0127		0.994	

to the continuous polymerization reaction by radicals with long lives. Variation of relation rate did not appear until after 72 h, and results of our experiment concur with that of Senden et al. [18]. Our findings provide evidence that the stability of the NIPAM polymer gel can persist up to 3 months post-irradiation.

Effects of monomer and crosslinker concentrations

Table 6 presents the mass fraction of bisacrylamide crosslinker ($\%C$) and the total mass fraction of monomers ($\%T$) in the recipe. Monomer concentration was within the range of 6.5−8.5$\%T$ in total mass fraction, while that of crosslinker was within 33.3−46.7$\%C$ for runs 1−9 in the present study. For comparison, we also present the characteristics of gel with various compositions for runs 10−16. Figure 4 illustrates the ratio of monomer and crosslinker concentrations $(\%C)/(\%T)$ and the corresponding linearity. Linearity was greater than 0.99 when $(\%C)/(\%T)$ was lower than 8.0, except for run 15. Thus, linearity can be divided into two ranges: high linearity range when $(\%C)/(\%T)$ is lower than 8.0 and low linearity range when $(\%C)/(\%T)$ is greater than 8.0. Figure 5 demonstrates that linearity was much higher when $(\%C)/(\%T)$ was around 5.5, which was the average of all linearity values for $(\%C)/(\%T)$ lower than 8.0. However, linearity was much lower for runs 10, 12, and 14, whose ratio of monomer and crosslinker concentrations $(\%C)/(\%T)$ were far from 5.5.

We observed that sensitivity and linearity were related to $\%T$, which is the total weight percent of monomer and crosslinker in the system, and to $\%C$, which is the concentration of the crosslinker in relation to the total monomer. Our findings are as follows:

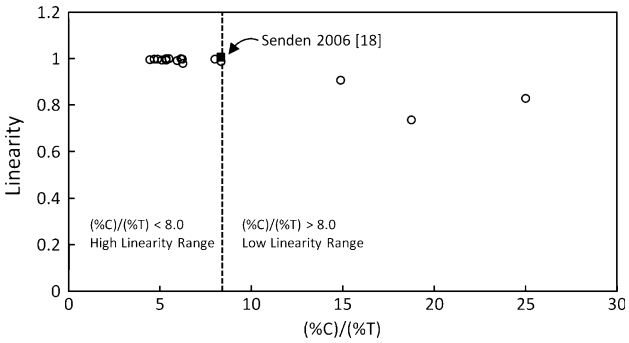

Fig. 4 Ratio of monomer and crosslinker concentrations $(\%C)/(\%T)$ and the corresponding linearity

(1) Increasing $\%T$ while maintaining constant gelatin amount and $\%C$ increased dose sensitivity and linearity. The linearity of sample gels was greater than 0.99 when $(\%C)/(\%T)$ was lower than 8.0.
(2) Increasing $\%C$ while maintaining constant gelatin amount with larger $\%T$ increased dose sensitivity. However, excessive $\%C$ causes crystal formation after preparation of gel from prior maximum solubility experiments, indicating the solubility limit of bisacrylamide. Sensitivity decreased with increasing $\%C$ up to the solubility limit of bisacrylamide. This concurs with findings of previous studies [21, 27]. Consequently, the optimal $(\%C)/(\%T)$ is within the range of 4−9.

Table 6 Effect of the ratio of monomer and crosslinker concentrations on sensitivity, linearity, and $(\%C)/(\%T)$

Run	Gelatin (%)	NIPAM ($\%T$)	Bis ($\%C$)	THPC (mM)	Sensitivity	Linearity	$(\%C)/(\%T)$
1	5.5	6.5	38.5	4.5	0.0279	0.99	5.923
2	5.5	7.5	40	5	0.0326	0.992	5.333
3	5.5	8.5	41.2	5.5	0.0336	0.996	4.847
4	6	7	42.9	5.5	0.0167	0.998	6.129
5	6	8	43.8	4.5	0.0274	0.998	5.475
6	6	7.5	33.3	5	0.0135	0.994	4.440
7	6.5	7.5	46.7	5	0.0159	0.997	6.227
8	6.5	7	35.7	5.5	0.0202	0.993	5.100
9	6.5	8	37.5	4.5	0.0261	0.996	4.688
10	4	2	50	5	0.0011	0.828	25.000
11	4	6	50	10	0.0254	0.986	8.333
12	5	4	75	20	0.0009	0.736	18.750
13	5	7.5	60	5	0.0236	0.997	8.000
14	6	5.5	81.8	10	0.0013	0.906	14.873
15	6	4	25	20	0.0015	0.979	6.250
16	6	7.5	40	5	0.0257	0.999	5.333

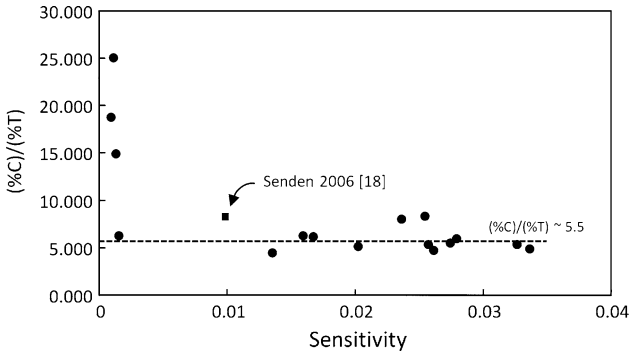

Fig. 5 Ratio of monomer and crosslinker concentrations $(\%C)/(\%T)$ and the corresponding linearity

(3) Since runs 2 and 3 had the best dose sensitivity among the nine groups, the optimal $(\%C)/(\%T)$ is within the range of 4.8−5.3, and the concentration of THPC is within the range of 5−5.5 mM by ratiocination. Similar results were reported by previous studies [19]. We reproduced the data from Senden et al. [18] for comparison in Figs. 4 and 5, which were consistent with our findings.

Conclusion

The present study adopted a systematic approach to determine the effect of gel composition on the dose response of NIPAM polymer gel. The main controllable factors are the amounts of gelatin, NIPAM, Bis, and THPC. The new and significant results presented in the present study are as follows: (1) The amount of each component, i.e., gelatin (59.73%), NIPAM (15.17%), Bis (10.64%), and THPC (14.45%), had dominant effects on the sensitivity of the gel. The amount of gelatin (44.70%) and Bis (50.99%) significantly affected the linearity of the gel; (2) The temporal stability experiment showed that the dose response curve attained stability at about 5 h after irradiation and persisted up to almost 3 months; (3) The linearity of most compositions of the gel was greater than 0.99 when $(\%C)/(\%T)$ was lower than 8.0; (4) The optimal $(\%C)/(\%T)$ for higher sensitivity is within the range of 4−9.

Future studies will focus on developing new gel recipes with other nontoxic monomers to make them suitable for different dose ranges. In addition, the optimal gel recipe for different dose ranges should be investigated in the future.

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