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A novel method for increasing the sensitivity of NIPAM polymer gel dosimeter

Vahid Anaraki[a], Seyed Mohammad Mahdi Abtahi[b,*], Bagher Farhood[c], Mahsa Ejtemai-fard[b]

[a] Medical Radiation Department, Islamic Azad University, Science and Research Branch, Tehran, Iran
[b] Physics Department, Imam Khomeini International University, P.O. Box 34149-16818, Qazvin, Iran
[c] Department of Medical Physics and Radiology, Kashan University of Medical Sciences, Kashan, Iran

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ABSTRACT

NIPAM polymer gel dosimeter has low toxicity and its response does not particularly depend on dose rate and beam energy. However, a chief drawback of the NPAM gel dosimeter is its relatively low sensitivity. In the current study, the sensitivity of the NIPAM gel dosimeter was improved by adding urea which this new formula gel dosimeter was called U-NIPAM (Urea and NIPAM) and optimal amount of urea for this new formula was evaluated. For this purpose, various concentrations of the urea (1%, 2%, 3% and 4% (w/w)) were tested. The samples were irradiated using 1.25 MeV and 6 MV photon energies and imaged by a 1.5 T MRI scanner. Then, the MRI response (R_2) and the sensitivity of the conventional NIPAM and U-NIPAM gel dosimeters with different percentages of urea were analyzed at a 0–6 Gy dose range, different post irradiation time, and temperature during scanning. The radiological properties of U-NIPAM polymer gel dosimeter reveal that this substance can be considered as a water/soft tissue equivalent material. With analyzing the findings, it was found that the optimal amount of urea is 3%, because after this concentration, the R_2-dose sensitivity of U-NIPAM gel dosimeter does not significantly changed ($P > 0.05$). Furthermore, the results showed that using 3% urea in conventional NIPAM gel formulation leads to a sensitivity increase of around 37% (0.242 vs. 0.177 s^{-1} Gy^{-1}). In addition, other results for optimized U-NIPAM gel dosimeter include: a) an excellent linear R_2-dose response in 0–6 Gy dose range, and b) stability in the R_2 value and the sensitivity for 18–21 °C temperatures.

1. Introduction

Dosimetry of ionizing radiation is a well-established and radiation therapy relies on this term for optimization of cancer treatment and reduction of adverse side effects for patients (Kron et al., 2016). Modern techniques used in this treatment modality like intensity modulated radiotherapy, volumetric modulated arc therapy, and stereotactic radiosurgery provide complex three dimensional (3D) conformal dose distributions; hence, in these techniques, accurate and precise measurement of dose delivered to target volume is one of the main aims in clinical dosimetry (Sellakumar and Samuel, 2010). On the other hand, true 3D verification of dose distribution is necessary for these complex techniques (Khezerloo et al., 2017a, 2018). However, previous methods of dosimetry measure dose distribution either single point (such as ion chambers, thermoluminescent dosimeters or diodes detectors) or 2D (such as diode array or film detectors) (Doran, 2009).

Gel dosimetry systems are considered as one of the true 3D dosimeters (Yan and Moros, 2005). These dosimeters are able to measure dose distribution in high dose gradient regions and in a radiation field with irregular shape (Oldham et al., 2003). According to chemical mechanism, gel dosimeters have been classified in three major groups including ferric dosimeters, polymer and radiochromic gel dosimeters (Khezerloo et al., 2017b).

Various types of gel matrices have been applied as tissue-equivalent media such as porcine gelatin (Gallo et al., 2018; Pappas et al., 2018; Del Lama et al., 2017), agarose (Soliman et al., 2017; Marrale et al., 2014; Gambarini et al., 2017), and poly-vinyl alcohol coupled with glutaraldehyde (PVA-GTA) (Collura et al., 2018; Marini et al., 2017; Marrale et al., 2017; Smith et al., 2015). Each of these dosimetry systems had its own advantages and limitations. For example, agarose is likely the most frequent gelling agent in ferric dosimeters; however, there is one main disadvantage for this gel substance, that is the ferric ions generated in the irradiated gel region are capable of diffusing within the dosimeter (Marrale et al., 2014). Or, PVA-GTA agent enable to obtain diffusion rates remarkable lower than those of gelatin and agarose (Gallo et al., 2018).

* Corresponding author.
E-mail addresses: smabtahi2007@gmail.com, sm.abtahi@sci.ikiu.ac.ir (S.M.M. Abtahi).

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In 1993, polymer gel dosimetry was introduced as a new dosimetric system that enables dose distribution measurements with high spatial resolution (Maryanski et al., 1993). Other advantages of these dosimeters are radiological tissue equivalence, independency to radiation direction, integration of dose during a treatment, etc. (Abtahi et al., 2014, 2016; Basfar et al., 2015). Polymer gel dosimeters are water-based gel matrix (80–90% of the dosimeter weight) which monomers are homogeneously distributed (Abtahi et al., 2016; Sedaghat et al., 2011). Irradiation induces water radiolysis and the generated radicals initiate the process of monomers' polymerization (Khezerloo et al., 2017b; Urbonavicius and Adliene, 2018). The amount of polymer produced is related to the absorbed radiation dose (Lotfy et al., 2017) and can be quantified by MRI technique or other imaging modalities (Baldock et al., 2010; Sellakumar et al., 2007).

In recent years, several studies have been conducted to improve polymer gel dosimeters. In this regard, different monomers (Senden et al., 2006; Trapp et al., 2005; De Deene et al., 2002a; Lepage et al., 2001), various antioxidants (De Deene et al., 2002b), and some additives like urea and glucose or gold nanoparticles (Abtahi et al., 2014; Rahman et al., 2012), etc. were used in structure of polymer gel dosimeters.

In 2006, Senden et al. (2006) developed a polymer gel dosimeter using N-isopropylacrylamide (NIPAM) monomer. This monomer has low toxicity (oral LD_{50} of 375 mg kg^{-1}) and superior water solubility. Furthermore, this gel dosimeter does not particularly depend on the changes of dose rate (Senden et al., 2006; Sigma-Aldrich, 2013). However, a chief drawback of the NPAM polymer gel dosimeter is its relatively low sensitivity. It is notable that slope of the linear region of the dosimeter response to absorbed dose values is considered as the sensitivity of a polymer gel dosimeter and is named the 'response–dose sensitivity'.

In the current study, sensitivity of the NIPAM gel dosimeter was improved by adding urea which this new formula gel dosimeter was called U-NIPAM (Urea and NIPAM). Furthermore, the optimal amount of urea for this new formula gel dosimeter was determined. Finally, temporal stability and temperature dependence of this gel dosimeter during scanning were investigated by using Magnetic Resonance Imaging (MRI) technique.

2. Materials and methods

2.1. Manufacture of U-NIPAM polymer gel

In the current study, the formulation of conventional N-isopropylacrylamide-based polymer gel was improved. The NIPAM gel dosimeter recipe of Senden et al. (2006) was considered as a basis and then urea was added to formula of this polymer gel to generate the new polymer gel (U-NIPAM).

The chemical ingredients of U-NIPAM gel include: High-pressure liquid chromatography (HPLC) grade pure water (Obtained from Direct-Q 3 UV water purification system, Millipore, France), gelatin (porcine skin, type A, 300 Bloom, Sigma Aldrich, USA), N-isopropylacrylamide (Sigma Aldrich, USA), N,N'-methylene-diacrylamide (Bis) (for molecular biology, for electrophoresis, ≥ 99.5%, Sigma Aldrich, USA), Tetrakis hydroxyl methyl phosphonium chloride (THPC) (80% solution in water, Sigma Aldrich, USA), and urea (Urea cryst. Extra Pure, Merck, Germany).

Chemical concentrations used in this study were listed in Table 1. The logic of choosing these concentrations in Table 1 was regard to the NIPAM gel formulation by Senden et al. (2006). The optimal formulation of the U-NIPAM polymer gel was characterized by considering the various amounts of urea. For this purpose, percentage weigh amounts of urea were selected in concentrations of 0%, 1%, 2%, 3% and 4% (w/w). Therefore, new gel formulations shown in Table 1 were manufactured in five rounds and in each round, the urea amount was changed. It is noteworthy that the amount of water used in the gel formula was reduced by the amount of urea added in each step, and the amount of rest of the chemical compounds was constant. Chemical structure of urea substance is shown in Fig. 1.

Table 1
Different conventional NIPAM and U-NIPAM polymer gel compositions and concentrations in five rounds.

	Round 1	Round 2	Round 3	Round 4	Round 5
Urea	0 wt%	1 wt%	2 wt%	3 wt%	4 wt%
Water	89 wt%	88 wt%	87 wt%	86 wt%	85 wt%
Gelatin	5 wt%	5 wt%	5 wt%	5 wt%	5 wt%
NIPAM	3 wt%	3 wt%	3 wt%	3 wt%	3 wt%
BIS	3 wt%	3 wt%	3 wt%	3 wt%	3 wt%
THPC	10 mM	10 mM	10 mM	10 mM	10 mM

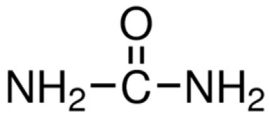

Fig. 1. Chemical structure of urea substance.

The U-NIPAM gel dosimeter was fabricated under a fume hood in normal atmospheric conditions. The fabricating method was similar to that method of previously described for manufacturing NIPAM polymer gel dosimeter (Senden et al., 2006). Briefly, at first, the urea amount was completely dissolved in 90% of the water at room temperature. While stirring continuously, the gelatin was swelled in the water at room temperature for 10 min, before being heated to 50 °C. Approximately 3 wt% of Bis was dissolved at 50 °C within 15 min while stirring the mixture was performed continuously. The N-isopropylacrylamide monomer was applied after the gelatin–cross linker mixture was cooled to almost 37 °C. THPC solution, as the antioxidant, was mixed with the 10% remnants of water, and was added to the solution (at temperature of about 35 °C). The resulted gel dosimeter was transparent and clear. The U-NIPAM polymer gel dosimeter solution was transferred into glass test tubes with length of 45 mm, dimension of 20 mm, and volume of 100cc, and the lids of the vials were fastened with screw caps and sealing films. After preparation, the gel tubes were cooled off gradually at room temperature and then stored at temperature of 4–7 °C in a refrigerator for 6–12 h.

2.2. Radiological properties of U-NIPAM polymer gel dosimeter

To evaluate radiological properties, the ratio of electron to mass density (ρ_e/ρ) and the effective atomic number (Z_{eff}) of U-NIPAM gel dosimeter were calculated. The electron density (ρ_e) of U-NIPAM gel dosimeter and its number of electrons per gram (n_e) were obtained by the following equations:

$$\rho_e = \rho . N_A . \sum w_i . \left(\frac{Z_i}{A_i}\right) \quad (1)$$

$$n_e = \left(\frac{\rho_e}{\rho}\right) \quad (2)$$

where N_A is Avogadro's number, w_i is weigh fraction of the i-th element of atomic number (Z_i) and atomic mass (A_i).

Also, Mayneord's formula (Khan, 2010) was used to calculate the Z_{eff} of U-NIPAM gel dosimeter:

$$Z_{eff} = \sqrt[2.94]{\sum_{i=1}^{n} a_i . Z_i^{2.94}} \quad (3)$$

where a_i is the relative electron fraction of the i-th element.