


Article

# Improved Dose Response of *N*-(hydroxymethyl)acrylamide Gel Dosimeter with Calcium Chloride for Radiotherapy

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**Abstract:** The impact of calcium chloride (CaCl<sub>2</sub>) on the performance of *N*-(hydroxymethyl)acrylamide (NHMA) polymer gel dosimeter is studied in this article. The dosimeter was exposed to doses of up to 10 Gy with radiation beam-energy of 10 MV and dose-rates of 300 cGy/min. The relaxation rate (R<sub>2</sub>) parameter was utilized to explore the performance of irradiated NHMAGAT gels. The dose response in terms of R<sub>2</sub> increased from 0.29 to 0.63 Gy<sup>-1</sup>·s<sup>-1</sup> with increasing calcium chloride concentration from 0 to 1000 mM. The results show no substantial impact of dose-rates as well as radiation energies on NHMAGAT samples. For the steadiness of irradiated NHMAGAT dosimeters, it was found that there is no apparent variation in R<sub>2</sub> (less than ±3%; standard deviation) up to 3 days. The overall uncertainty of the gel dosimeter with calcium chloride is 4.96% (double standard deviation, 95% confidence level).

**Keywords:** polymer gel; *N*-(hydroxymethyl)acrylamide; calcium chloride; nuclear magnetic resonance; dosimetry



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## 1. Introduction

New developments in radiotherapy have been concerned with the study of equivalent gel dosimeters for tissues containing active chemical sensors to measure the absorbed radiation dose [1–6]. Gel dosimeters such as polymer gels have a range of properties like biological tissues, and are suitable alternatives compared with conventional dosimeters due to their ability in resolving three-dimensional (3D) dose distributions [7–11].

Polymer gels have an electron density that is like tissue-equivalent material [12–14]. It contains monomers that polymerize during ionizing radiation [15,16]. The first recipe was fabricated from *N*, *N*'methylene-bis-acrylamide and acrylamide [17,18].

The complex radiation dose response recorded in polymer gels (i.e., degree of polymerization) can be explored in 3D utilizing various modalities such as MRI and optical techniques [18–20]. The interaction between monomers in the gel after irradiation leads to drops in the mobility of H<sub>2</sub>O molecules and decreases in the relaxation time (T<sub>2</sub>) values in the MRI technique [21–24]. These alterations of the transverse relaxation rate (R<sub>2</sub> = 1/T<sub>2</sub>) can be measured via NMR relaxometry [25,26].

Different types of monomers were incorporated in the preparation of various types of polymer gels, such as *N*-isopropylacrylamide [27], methacrylic-acid [28,29], *N*-hydroxyethylacrylate [30], *N*-vinylpyrrolidone [31–33], Itaconic-acid [34], 2-acrylamide-2-methylpropane-sulfonic-acid sodium salt [35], *N*-(3-methoxypropyl)-acrylamide [10,36], and *N*-(hydroxymethyl)-acrylamide [8,37–39].

Many works have reported the influence of different salts on the performance of gel dosimeters. The literature shows a significant effect of specific inorganic salts on the dose response of irradiated gels [38–42]. The polymerization of polymer gels has been dramatically increased and enhanced by the addition of inorganic salts that attract water molecules and other elements via electrostatic interactions in the gel, leading to an increase in the rate of polymerization [40]. Rabeah et al. (2017) [37] introduced the composition of a polymer gel that contains *N*-(hydroxymethyl)acrylamide monomer (NHMA). The evaluation of irradiating this polymer gel was carried out by NMR and spectrophotometry. The data show a good response to ionizing radiation.

In this work, the major objective is to increase the dose sensitivity for formulations of NHMA gel samples by adding an appropriate concentration of salt, calcium chloride ( $\text{CaCl}_2$ ). The influence of temperature during scanning, dose-rates, radiation energies and the stability of irradiated samples were also examined and reported.

## 2. Materials and Methods

### 2.1. Samples Preparation

NHMAGAT samples were fabricated in normal conditions as the previous gel of normoxic polymer gel [12]. This polymer gel has five main components: NHMA (8 wt%) and *N,N*-methylene-bis-acrylamide (3 wt%) as a co-monomers, gelatin-type A (4 wt%) as a gel matrix, tetrakis (hydroxymethyl) phosphonium chloride-THPC (20 mM) as an oxygen scavenger, and a wide concentration range of calcium chloride (0–1000 mM) as an additive. The chemicals were purchased from Sigma-Aldrich chemical company (St. Louis, MO, USA). NHMAGAT polymer gels were fabricated as follows: at room temperature, gelatin-type A was added to the deionized-water and stirred for 5 min, Then, the temperature of mixture was increased to 48 °C for one hour using a hot-plate magnetic stirrer. Then, the NHMA, BIS, and  $\text{CaCl}_2$  were added and stirred until a homogenous solution had been obtained. After that, THPC was added to the solution at 35 °C and the solution was stirred for about 2 min. The prepared solutions were poured into air-tight NMR glass tubes (10 mL) and kept in a fridge for 24 h before X-ray irradiation.

### 2.2. Irradiation

The prepared gels were placed in a cubic water tank ( $30 \times 30 \times 30 \text{ cm}^3$ ) and exposed to various absorbed doses at standard parameters of (5 cm depth, 100 source to surface distance and  $20 \times 20 \text{ cm}^2$  field size) using 10 MV Linac X-ray beam (Elekta, Laurent Leksell, Stockholm, Sweden) with a 300 cGy/min dose-rate. The impact of dose-rates and radiation energies were examined by irradiating the gel dosimeters at a fixed beam energy of 10 MV with 150 and 600 cGy/min and at a fixed dose-rates of 300 cGy/min with 6 and 15 MV. Three gels were exposed at certain absorbed doses, and the average values are shown in the Results and Discussion section.

### 2.3. Nuclear Magnetic Resonance (NMR) Measurements

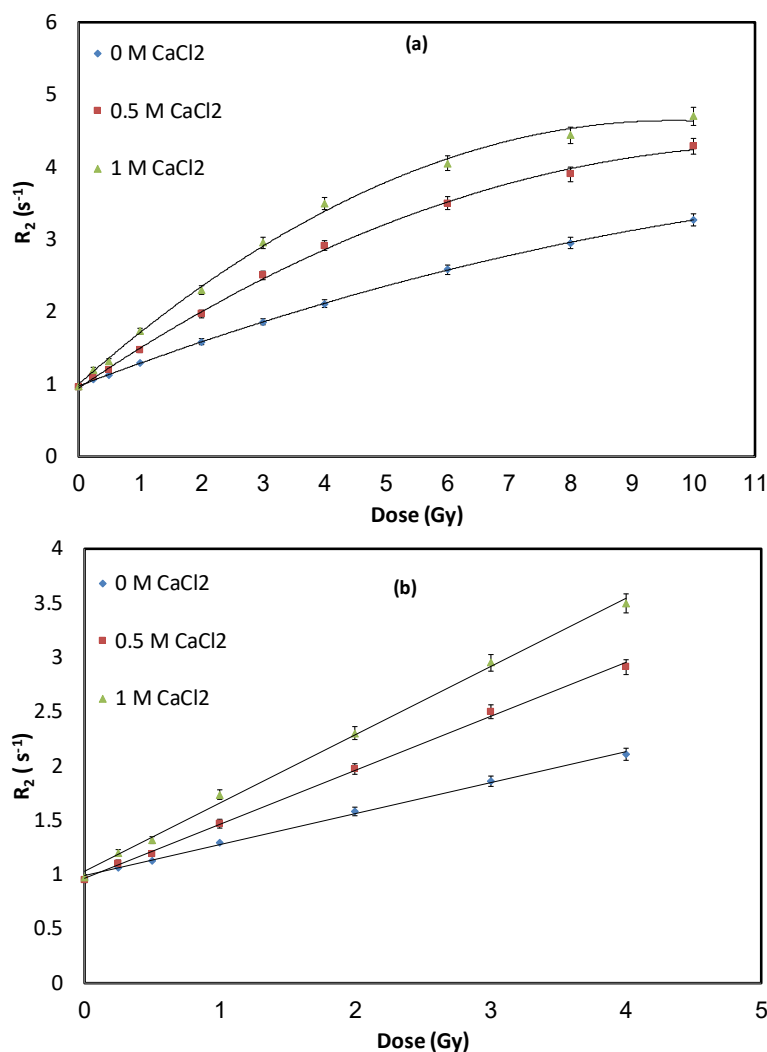
The prepared samples were placed into a water-bath system (Julabo, Seelbach, Germany), which was connected to an NMR relaximeter to control the scanning temperature during NMR measurement from 10 to 30 °C. The NMR samples were read out using the 0.5 T NMR technique (Bruker, Bremen, Germany) under a fixed scanning temperature of 20 °C. The relaxation rate ( $R_2$ ) values of the measured gels were calculated by a standard Multi-Spin-Echo sequence (Carr Purcell Meiboom Gill (CPMG)) at 0.4 ms echo-time spacing and 2000 echoes. Three gels were read out at certain absorbed doses, and the average values as well as standard deviations are included in the Results and Discussion section.

## 3. Results and Discussion

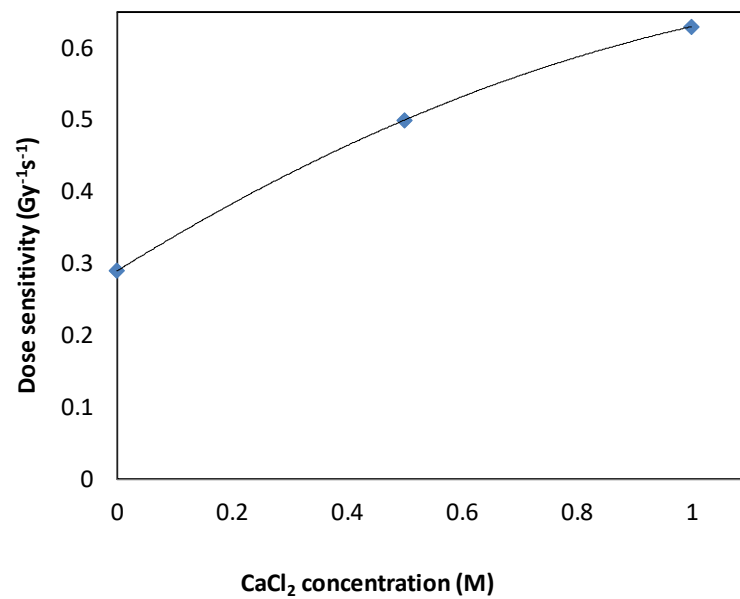
### 3.1. Impact of Calcium Chloride ( $\text{CaCl}_2$ ) Concentration

Different compositions of NHMAGAT gel dosimeters, with different concentrations of  $\text{CaCl}_2$ , were prepared to evaluate the impact of salt on the dose response and dose sensitivity

of NHMAGAT dosimeters. A set of three samples from different gel batches were used for each formulation code in all absorbed dose points. Figure 1 shows the relationship between the relaxation rate and the dose amount, which proves that  $\text{CaCl}_2$  did not increase the background value of the unirradiated NHMAGAT dosimeter. Additionally, these curves of NHMAGAT samples show a remarkable increase in  $R_2$  with an absorbed dose up to 10 Gy because of increasing the polymerization of the NHMAGAT gel. When the  $\text{CaCl}_2$  concentration changes from zero to 1000 mM, the relaxation rate increases proportionally. This can be clarified by the hypothesis presented by Hayashi, which states that inorganic salts such as  $\text{CaCl}_2$  increase the temperature of gels during irradiation, and as a result, the exothermic polymerization rate increases, which improves the dose sensitivity [40]. To override the effect of salt on the reduction in the melting point of the prepared gel [43], a double amount of the antioxidant (20 mM) was used. Additionally, in Figure 1, the intercept is related directly to the gel matrix [22]. In contrast, the sensitivity obtained from the slope of linear fit was found from the slope of the linear part in the  $R_2$  dose graph, which determines the dose resolution [44,45]. The  $R_2$  curves are approximated by linear-fit in a dose-range of 0–4 Gy (see Figure 1b). Beyond 4 Gy, the response changes towards the saturation region due to the increase in the consumption rate of co-monomers after adding salt (Figure 1a). The sensitivity increases strongly when the  $\text{CaCl}_2$  concentration is increased from 0 to 1000 mM (see Figure 2 and Table 1).



**Figure 1.**  $R_2$  of gels with various concentrations of  $\text{CaCl}_2$  when irradiated at doses up to (a) 0–10 Gy, and (b) 0–4 Gy. Error bars are the  $2\sigma$  of  $R_2$  values.



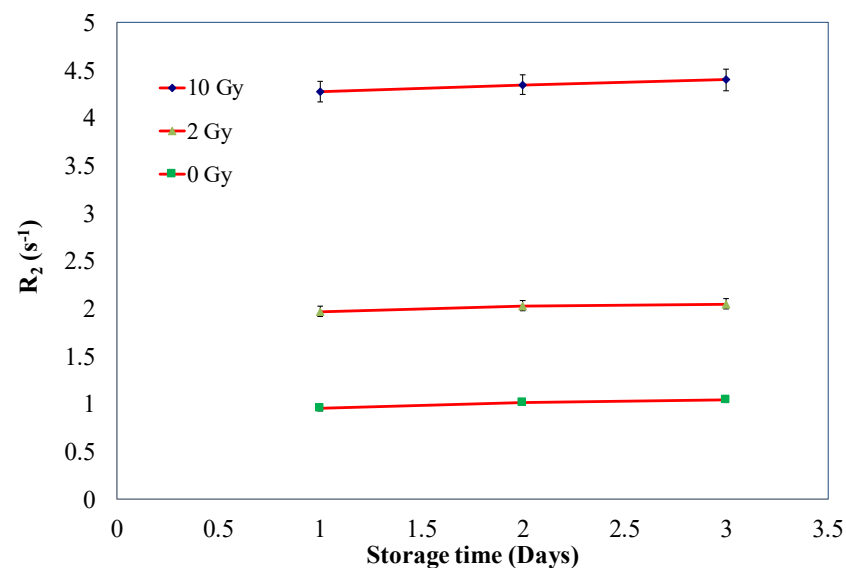
**Figure 2.** Dose sensitivity value for different CaCl<sub>2</sub> concentrations.

**Table 1.** Linear equations and sensitivities of curves in Figure 1b.

Linear Equations	Sensitivity (Gy <sup>-1</sup> ·s <sup>-1</sup> )	Recipe
$R_2 = 0.29D + 0.99$	0.29	NHMAGAT (1)
$R_2 = 0.50D + 0.96$	0.50	NHMAGAT (2)
$R_2 = 0.63D + 1.03$	0.63	NHMAGAT (3)

### 3.2. Stability of NHMAGA Dosimeters

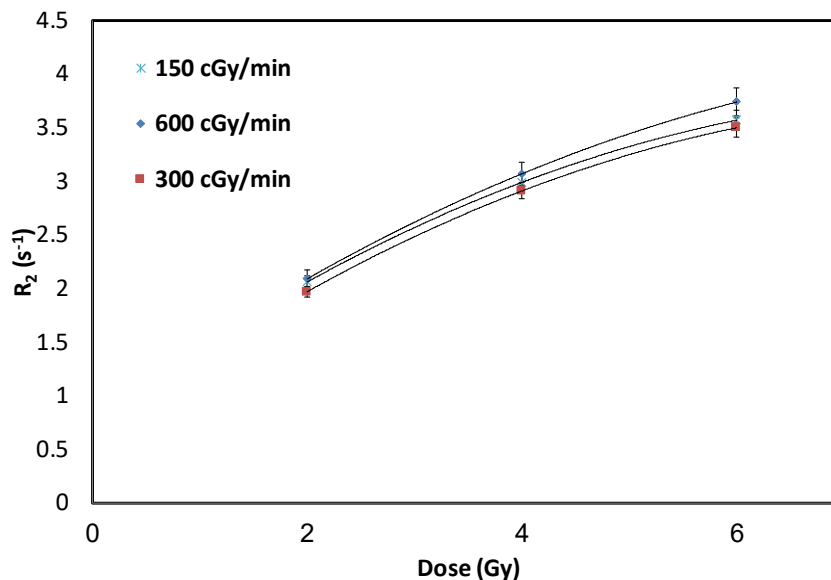
The NHMAGAT (2) gel dosimeter was irradiated at three different doses and kept in a fridge for three days to study the effect of post-irradiation stability. Three gels for each dose were used, and the average values are presented. The samples were read out daily for 3 days, which is quite suitable for routine dose calibration. The results are shown in Figure 3, from which it is evident that there is no significant change in  $R_2$  after up to 3 days.



**Figure 3.**  $R_2$  of gel with 500 mM CaCl<sub>2</sub> irradiated at different doses as a function of storage time. Error bars are the  $2\sigma$  of  $R_2$  values.

### 3.3. Influence of Dose-Rates

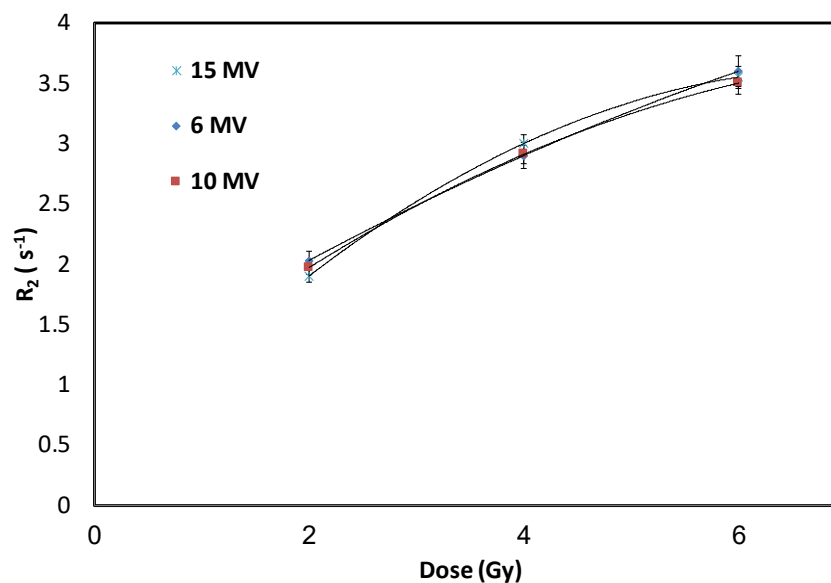
NHMAGAT with 500 mM  $\text{CaCl}_2$  was used to investigate the influence of dose-rates, i.e., 150, 300 and 600 cGy/min, with a constant radiation energy of 10 MV. These gel samples were exposed to various doses of 2, 4, and 6 Gy. To report the standard deviations, a set of three gels were exposed to each selected dose. Figure 4 shows no significant effect of dose-rates on this polymer gel dosimeter.



**Figure 4.**  $R_2$  of gel with 500 mM  $\text{CaCl}_2$  for various dose-rates under 10 MV radiation energy. Error bars are the  $2\sigma$  of  $R_2$  values.

### 3.4. Effect of Radiation-Energies

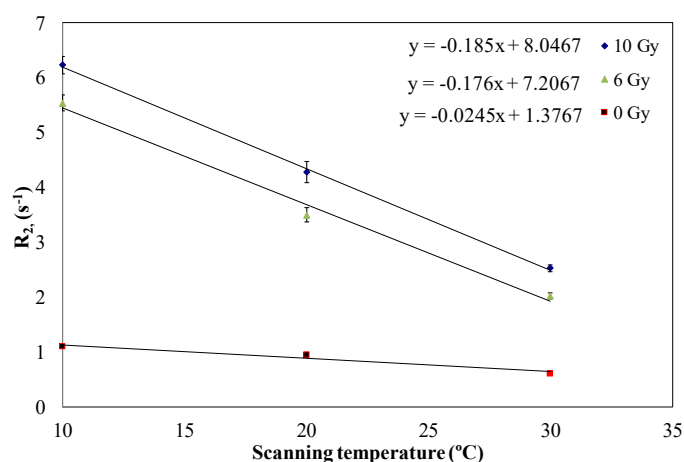
The impact of radiation energies on the performance of NHMAGAT with 500 mM  $\text{CaCl}_2$  was studied by exposing the gel to three different values of radiation energy at dose-rates of 300 cGy/min. These gels were exposed to different absorbed doses. The results in Figure 5 show that there is little influence of radiation dose on this polymer gel.



**Figure 5.**  $R_2$  of gel with 500 mM  $\text{CaCl}_2$  for various radiation energies. Error bars are the  $2\sigma$  of  $R_2$  values.

### 3.5. Effect of Scanning Temperature

Samples of formulation code NHMAGAT (2) were scanned at different temperatures. Figure 6 illustrates that the response increases with the cooling of the samples during the NMR scanning. This significant change in NMR readout is due to the alteration in the magnetization values between the protons of the semi-solid and aqueous phase that regulate the relaxation time of H<sub>2</sub>O in the gel, which is enhanced with declining scanning temperature [46–48].



**Figure 6.** Relaxation rate of unirradiated and irradiated gels with 500 mM CaCl<sub>2</sub> exposed to 6 and 10 Gy as a function of scanning temperature. Error bars are the 2σ of R<sub>2</sub> values.

### 3.6. Uncertainty Analysis

The overall uncertainty budget for the dosimeter was calculated based on different parameters of uncertainty. These parameters are the calibration of the radiotherapy unit with the ionization chamber (1.2%), batch uniformity (1.4%), reproducibility of measurements (1.1%), MNR sensitivity variation (0.3%), calibration curve fit (1.2%), and temporal stability (0.2%) [2,49].

The calculated total dose of uncertainty is defined as the combined uncertainty multiplied by two for a confidence level of 95% [49]. The square root of the sum of all uncertainty components is equal to the combined uncertainty [49]. Therefore, the combined uncertainty is 2.48% and the calculated overall uncertainty for R<sub>2</sub> measurements is 4.96%. These values are considered sufficient for the estimation of dose distributions in radiotherapy.

## 4. Conclusions

An improved composition of polymer gel dosimeter has been introduced as a normoxic polymer gel *N*-(hydroxymethyl)acrylamide (NHMAGAT) for radiotherapy by the addition of CaCl<sub>2</sub> inorganic salt. The results of the NHMAGAT gel dosimeter in this study show that the response to the dose increases strongly with increasing CaCl<sub>2</sub> concentration from 0 to 1 M. The unirradiated and irradiated developed gel samples were almost stable after up to 3 days. No appreciable effect was observed on the performance of irradiated NHMAGAT gel dosimeter when changing the dose-rates or radiation energies. The response increases strongly upon cooling the gel during NMR measurement. Overall, the data suggest strongly that CaCl<sub>2</sub> acts as an excellent sensitizer to the polymerization of irradiated dosimeters.

**Author Contributions:** Conceptualization, K.A.R., M.M.E., I.M.E.H. and M.T.M.S.; Data curation, K.A.R. and R.E.A.-T.; Formal analysis, K.A.R. and R.E.A.-T.; Funding acquisition, K.A.R.; Investigation, K.A.R., M.M.E., I.M.E.H. and M.T.M.S.; Methodology, K.A.R. and R.E.A.-T.; Project administration, K.A.R.; Supervision, K.A.R. and M.T.M.S.; Writing—original draft, K.A.R., M.M.E., I.M.E.H. and M.T.M.S.; Methodology, K.A.R. and R.E.A.-T.; Writing—review & editing, K.A.R., M.M.E., I.M.E.H. and M.T.M.S.; Methodology, K.A.R. and R.E.A.-T. All authors have read and agreed to the published version of the manuscript.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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