Improved MAGIC gel for higher sensitivity and elemental tissue equivalent 3D dosimetry

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(Received 20 April 2009; revised 22 September 2009; accepted for publication 13 October 2009; published 8 December 2009)

Purpose: Polymer-based gel dosimeter (MAGIC type) is a preferable phantom material for PET range verification of proton beam therapy. However, improvement in elemental tissue equivalency (specifically O/C ratio) is very desirable to ensure realistic time-activity measurements.

Methods: Glucose and urea was added to the original MAGIC formulation to adjust the O/C ratio. The dose responses of the new formulations were tested with MRI transverse relaxation rate (R2) measurements.

Results: The new ingredients improved not only the elemental composition but also the sensitivity of the MAGIC gel. The O/C ratios of our new gels agree with that of soft tissue within 1%. The slopes of dose response curves were 1.6–2.7 times larger with glucose. The melting point also increased by 5 °C. Further addition of urea resulted in a similar slope but with an increased intercept and a decreased melting point.

Conclusions: Our improved MAGIC gel formulations have higher sensitivity and better elemental tissue equivalency for 3D dosimetry applications involving nuclear reactions. © 2010 American Association of Physicists in Medicine. [DOI: [10.1118/1.3260844](https://doi.org/10.1118/1.3260844)]

Key words: gel dosimeter, proton therapy, positron emission tomography

I. INTRODUCTION

Range verification is very important in high-precision proton (or other heavy ion) beam therapy. During proton therapy, small amounts of positron emitters, such as ^{11}C ($T_{1/2}=20.39$ min), ^{13}N ($T_{1/2}=9.965$ min), ^{15}O ($T_{1/2}=2.037$ min), and ^{38}K ($T_{1/2}=7.636$ min) are produced along the beam path via different channels of nuclear fragmentation reactions, most importantly (p, pn) reactions.^{1–8} Positron emission tomography (PET) imaging of thus endogenously generated radionuclides (most importantly ^{11}C and ^{15}O) is the only practical approach for *in vivo* range verification of proton (or other heavy ion) beam therapy. To date, the most commonly used phantom materials for the PET monitoring of heavy ion (including proton) therapy include polymethyl methacrylate (PMMA),^{1,4–6} polyethylene, and gelatinous water (99% pure water).^{9,10} However, the elemental compositions of those materials (specifically the O/C ratio) are very different from tissue composition, leading to different rates of $^{15}\text{O}/^{11}\text{C}$ productions in the phantom. Because of the large difference in ^{15}O and ^{11}C half lives, for PET imaging started during or immediately after proton therapy, the time-activity curves measured with these types of phantom materials are very different from expected tissue response. Another rel-

evant but noncritical element is nitrogen, which will result in a small quantity of ^{13}N during proton irradiations (estimated initial yield <3% of total activity by Monte Carlo simulation studies⁸). In addition, dose distribution and actual proton range cannot be directly measured in such phantoms.

A polymer gel dosimeter is a preferable phantom material for this application. The three-dimensional (3D) dose distribution can be recorded in a gel phantom and imaged with magnetic resonance imaging (MRI),¹¹ therefore actual proton range can be measured directly and related to PET measured activity distal fall-off positions. Moreover, polymer gels have a better elemental tissue equivalency compared to other materials. Fong *et al.*¹² introduced the first normoxic gel formulation, the methacrylic and ascorbic acid in gelatin initiated by copper (MAGIC) gel. The O/C ratio of the MAGIC gel (10.68) is much closer to that of typical soft tissue (4.95) when compared with PMMA (0.53), but there is still a difference by a factor of 2, and further improvement is very desirable.

We have adjusted the elemental composition of MAGIC gel by adding a carbon-rich ingredient, glucose, and a nitrogen-rich ingredient, urea, to obtain an O/C ratio similar to soft tissue. The dose responses of the new formulations

TABLE I. Gel dosimeter formulations (in grams per 50 g of gel).

Formulation code ^a	Round 1			Round 2			Round 3		
	A	B	C	A	D	E	A	D	F
Water	42.9	33.8	33.7	42.9	33.4	33.1	42.9	33.4	32.7
Glucose	0	9.1	9.1	0	9.1	7.45	0	9.1	7.45
Urea	0	0	0	0	0	2.35	0	0	2.35
Hydroquinone	0.1	0.1	0.2	0.1	0.5	0.1	0.1	0.5	0.5
Preparation to irradiation		2 days			14 days			1 day	
Irradiation to MRI		5 days			8 days			1 day	

^aOther ingredients (same for all formulations): Gelatin (4.0), ascorbic acid (0.0176), methacrylic acid (3.0), and copper sulfate (0.000375).

were tested by x-ray irradiations followed by transverse relaxation rate (R2) measurements with MRI imaging. The melting points and densities of the modified gel dosimeters were also measured.

II. METHODS

II.A. Gel preparation

Gel formulations shown in Table I were prepared in three rounds. In the text, tables, and figures hereafter, a capital letter in a pair of brackets denotes the formulation code as shown in Table I.

The gel ingredients include: High-pressure liquid chromatography grade pure water, gelatin (300 bloom type A), glucose, ascorbic acid, copper sulfate, methacrylic acid (MMA), hydroquinone (all above from Sigma-Aldrich, St. Louis, MO) and urea (VWR international, West Chester, PA). The original 6% MAGIC gel formulation with modified copper sulfate concentration (A) was manufactured with each round as a control. Since higher concentration of copper sulfate in the gel has been shown to result in lower sensitivities and higher saturation doses,¹³ we used a lower concentration (0.0075 g/1000 g) than in the original formulation (0.02 g/1000 g).

In (B), glucose was added to the original gel to adjust the carbon composition. The hydroquinone (a free radical scavenger) concentration was increased in (C) and (D) to absorb additional free radicals introduced by glucose. In (E), both glucose and urea were added to adjust both the carbon and nitrogen compositions. In (F), a higher concentration of hydroquinone was added to (E).

Gels were prepared with the following procedures: Fresh solutions of copper sulfate (0.0005 g/ml) and ascorbic acid (0.0176 g/ml) were prepared before each round. For each 50 g of gel, 0.75 ml of copper sulfate and 1 ml of ascorbic acid were added later. Glucose and urea, if used, were first completely dissolved in water (subtracting the amount in the copper sulfate and ascorbic acid solutions) at room temperature, and gelatin was then added. The mixture was heated to 48 °C and stirred with a magnetic bar until gelatin was completely melted. Hydroquinone was then added in the mixture, still stirred, and the heater was turned off. Ascorbic acid and copper sulfate solutions were added when the mixture was cooled to ~37 °C. After 2 min, MAA was added and the gel

mixture was stirred for one more minute. The gel was then transferred into 5 ml glass vials, sealed with screw-cap tops and placed in a refrigerator until irradiation. The time between gel preparation and irradiation was two days for round #1, 14 days for round #2, and one day for round #3.

To test the melting points of the gels, small quantity of gels from each formulation was allowed to set on the side wall of a small glass jar. After thermal equilibrium with room temperature, the jars were put in a slowly heated water bath with the water temperature monitored by a thermometer. The melting point was considered as the water bath temperature at which the gels start melting so that the side wall of glass jars can no longer hold the gels. The densities of the gels were measured by filling a glass vial of known volume with gels, and weighing the vial before and after filling.

II.B. Gel irradiation

The gels were irradiated with a 6 MV x-ray beam using a Varian iX linear accelerator in the Department of Radiation Oncology at Massachusetts General Hospital (MGH), Boston, MA. The vials were irradiated in a water tray with a dose rate of 500 cGy/min. Doses of 0.5, 1, 3, 5, 10, and 20 Gy were delivered. All samples were returned to the refrigerator after irradiation until MRI imaging. The time between irradiations and MRI imaging was five days for round #1, eight days for round #2, and one day for round #3.

II.C. MRI

All the samples were imaged on a Siemens Trio 3-T MRI system with two single spin-echo sequences with a repetition time TR=4 s, echo times TE=7.3 and 60 ms, and slice thickness of 5.0 mm. Round #1 was imaged with a head coil and a pixel size of 1.7×0.9 mm², and rounds #2 and #3 were imaged with the body coil and a pixel size of 2.3×1.2 mm². The transverse R2 (1/T2) was calculated pixel by pixel with a two-point method¹⁴

$$R2 = (\ln S_1 - \ln S_2) / (TE_2 - TE_1), \quad (1)$$

where S_i and TE_i are the signal intensity and the echo time (TE) in image i . The mean R2 values and standard deviations were calculated for gel areas of each delivered dose.

TABLE II. Elemental compositions and physical properties of gels in Table I.

Medium	H (%)	C (%)	N (%)	O (%)	O/C	O/N	C/N	ρ (g/cm ³)	MP (°C)
Soft tissue ^a	10.2	14.3	3.4	70.8	4.951	20.8	4.21	1.06	–
Gel A ^b	10.5	7.65	1.28	80.38	10.51	62.8	5.98	1.06	32
Gels B, C, D ^c	9.71	14.9	1.28	73.9	4.952	57.77	11.67	1.13	37
Gels E, F ^d	9.65	14.55	3.47	72.17	4.960	20.79	4.190	1.13	30

^aData from ICRU Report 44 (1989) (Ref. 15).^bOriginal 6% MAGIC gel.^c6% MAGIC gel with glucose.^d6% MAGIC gel with glucose and urea.

III. RESULTS

III.A. Elemental compositions and physical properties

Table II shows the gel compositions of four major elements in soft tissue: Hydrogen, oxygen, carbon, and nitrogen. The O/C ratio of the original 6% MAGIC gel was 10.51, two times higher than that of typical soft tissue. After adding 18.2% (w/w) glucose while keeping other ingredients (except water) at the same level, the O/C ratio (gels B, C, and D) can be adjusted to the same level of that of soft tissue, but the nitrogen level was still lower. When both glucose and urea were added, the O/C, O/N, and C/N ratios all agreed with those of soft tissue within 0.5%. The absolute compositions of the four major elements agreed with those of soft tissue within 5%.

The density of the original MAGIC gel was the same as that of soft tissue. When glucose and urea were added, the density increased 6.6%. The melting point of the original MAGIC gel was 32 °C. Adding glucose increased the melting point to 37 °C. When both glucose and urea were added, the melting point was decreased to 30 °C.

III.B. Dose response

The dose response curves are shown in Fig. 1. In round #1, the slope increased by a factor of 2.7 when glucose was added into the original MAGIC gel (B). The intercept also increased from 22.66 (A) to 29.39 s⁻¹ (B) with the same hydroquinone concentration. When the hydroquinone concentration was doubled (C), the intercept decreased to 25.14 s⁻¹, while the slope was still 2.6 times higher compared to the original MAGIC gel (A).

In round #2, the dose response slope with glucose and a high (five times) hydroquinone concentration (D) is 2.2 times that of (A), while the intercept was further reduced to 22.85 s⁻¹. When urea was added (E), the slope remained higher [2.4 times than that of (A)], but the intercept also increased significantly, from 18.85 to 34.18 s⁻¹.

In round #3, a high (five times) hydroquinone concentration was added to the gel with glucose and urea (F), but the intercept was not reduced (34.53 s⁻¹). The slope again was higher (2.3 times) than that of (A). In the repeated batch of (D), the slope was 1.6 times that of (A), and the intercept was very close to that of (A) (22.20 vs 21.99 s⁻¹).

The measured dose response slopes, intercepts and their ratios are listed in Table III. Fong *et al.*¹² has pointed out that an important determinant of the sensitivity to detect small dose changes is the slope-to-intercept ratio of the dose response curve. When this ratio is considered, the sensitivity of the MAGIC gel is also improved by adding glucose, but the improvement was partially reversed by adding urea.

IV. DISCUSSION

A proton has a finite range in the tissue and deposits most of its energy near the end of its track. Therefore, proton therapy is able to deliver highly conformal radiation dose distributions to the tumor target volume, and is a favorable treatment modality for tumors with irregular shapes and near critical organs. However, uncertainties in dose delivery can result from different sources, including treatment planning errors, beam delivery, or patient positioning errors, organ motion, or for fractionated dose delivery, anatomic changes as a response to previous fractions. Proton range uncertainties are particularly of concern because of the large gradients of delivered dose near the Bragg peak. Verification of beam delivery within the patient is very important in this high-precision modality to ensure the treatment planning and delivery systems are functioning properly.^{1,2}

PET imaging is the only practical approach for *in vivo* range verification of proton (or other heavy ion) beam therapy,^{1,5,6} and is being actively investigated in several proton and heavy ion (carbon) treatment facilities. For clinical studies at MGH, a patient usually is scanned for 30 min after beam delivery,² either at a nearby PET/CT scanner within ~15 min walking distance, or at an in-room mobile PET scanner immediately after irradiation (most recently). Since proton-induced activity distribution is not directly related to dose distribution, current research is focused on range verification only, by comparing the fall-off positions of activity and dose-profiles along the beam path.¹⁻⁸ In current phantom studies using PMMA or other material, since dose distributions cannot be directly measured in the phantom, usually Monte Carlo simulated dose distribution is used instead. Moreover, the time-activity behavior is very different between PMMA and tissue responses, which will greatly affect the counting statistics and acquisition-time optimization for PET acquisitions started during or immediately after beam

FIG. 1. (a) Dose response curves of different gel formulations in Table I was the original MAGIC gel. In (b), (c), and (d) glucose was added to adjust the O/C ratio. In (e) and (f), both glucose and urea were added to adjust relative oxygen, carbon, and nitrogen compositions.

delivery. Figure 2 shows the expected time-activity responses of PMMA, the original, and modified gels. Because of lower ^{11}C and higher ^{15}O contents, proton-induced activity in tissue is relatively higher at the beginning and decays much faster compared to PMMA. The original MAGIC gel has a lower response at later time frames. The time-activity re-

sponses of modified gels are very similar to that of soft tissue for all time frames.

Our initial motivation of adding glucose and urea into the original MAGIC gel formulation was to improve its elemental tissue equivalency, specifically the O/C ratio. However, we have found that glucose improved not only the tissue equivalency but also the sensitivity of the gel. It has been reported that glucose accelerates the free radical polymerization rates of styrene monomers.¹⁶ Glucose may increase the sensitivity of the MAGIC gel system through the same mechanism. Although the reason is unknown,¹⁶ it might be related to the increased viscosity and/or the reducing property of glucose.¹⁷ Therefore for gel developments seeking improved dose sensitivity, adding glucose could be considered.

It has been reported that the dose response of a specific gel is affected by various factors including its heating and cooling history, the time between gel manufacture and irradiation and between irradiation and MRI imaging, the temperature at the times of irradiations and scans, and MRI scanner field strength.¹⁸ Therefore, the absolute values of dose response slopes should not be compared for different gel batches even if the same formulation is used. In our experiments, we prepared, irradiated, and scanned each round of gel samples side by side so that dose response variations caused by environmental factors were kept at a minimum, mainly from the manufacturing process. Formulations were compared within each round only.

We have observed a consistent improvement in the gel dose response when glucose was added to the original MAGIC formulation. The slope of dose response curve increased 1.6 to 2.7 times with glucose. Although the intercept was also larger, the slope-to-intercept ratio was still improved, and the intercept can be successfully reduced by increasing the concentration of hydroquinone, a free radical scavenger. Glucose also improved the linearity of most dose response curves. The average correlation coefficient (R) for linear least-squares fitting was 0.9855 for the original MAGIC gel, and 0.9906 for gel formulations with glucose (but not urea) added. Please note the $R2$ intercepts in our measurements were larger than that of Fong et al.¹² since we were using a single spin-echo sequence for $R2$ measurements.

Temperature is an important factor that could limit the wider use of a gel dosimeter because 3D information recorded in the gel would be lost if the gel melts. Other investigators have added formaldehyde to increase the melting point of MAGIC gels.¹⁹ We found that when glucose was added, the melting point of the gel increased 5°C , which would allow its convenient uses in most air-conditioned treatment rooms without introducing additional toxicity. The only drawback was a slightly increased gel density, which is still closer to tissue density when compared to PMMA, and is considered very acceptable in our application. For applications that elemental tissue equivalency is less important, the glucose concentration can be reduced to generate a gel with tissuelike density.

When both glucose and urea were added, the sensitivity

TABLE III. Slopes and intercepts of R2 dose response curves of gels in Table I.

Formulation code	Round 1			Round 2			Round 3		
	A	B	C	A	D	E	A	D	F
Slope (s^{-1}/Gy)	0.367 ± 0.035	0.978 ± 0.056	0.962 ± 0.048	0.501 ± 0.030	1.124 ± 0.048	1.21 ± 0.10	0.535 ± 0.036	0.878 ± 0.054	1.21 ± 0.11
Intercept (s^{-1})	22.66 ± 0.32	29.39 ± 0.38	25.14 ± 0.38	18.85 ± 0.22	22.85 ± 0.35	34.18 ± 0.50	21.99 ± 0.31	22.20 ± 0.41	34.53 ± 0.53
Slope-to-intercept ratio (Gy^{-1})	0.016 ± 0.002	0.033 ± 0.002	0.038 ± 0.002	0.026 ± 0.002	0.049 ± 0.002	0.035 ± 0.003	0.024 ± 0.002	0.040 ± 0.003	0.035 ± 0.003

was decreased when compared with adding glucose alone and the melting point was also lower. The decrease in sensitivity was mainly caused by increased intercepts of the dose response curves, while the slope remained more than two times higher than that of the original gel. It is interesting to note that when glucose was added, the increase in intercept was observed as an increased level of initial fogging in non-irradiated samples, and can be reduced by adding a higher concentration of a free radical scavenger. With urea, although the intercept was much larger and not responsive to additional free radical scavenger, the initial fogging was actually reduced by visual inspection, resulted in a very clear gel before irradiation. Therefore, the increase in intercept with urea was likely caused by the changed R2 of the gel matrix, rather than by the increased initial spontaneous polymerization of MMA monomers as in the glucose-only case. The possible reason is urea, as a general protein denaturant, unfolds gelatin proteins and alters their three-dimensional structures. Consequently, some proteins are irreversibly altered upon interaction with urea solutions,²⁰ and the MRI properties of the gel matrix are changed as well. The lack of initial fogging indicates that urea may actually inhibit the initial spontaneous polymerization of the gel. Gel dose response can also be measured by optical CT imaging,²¹ which maps the 3D optical density distributions in gel phantoms. If optical CT, rather than MRI, is used for gel readout, it is very

likely that gel sensitivity in terms of slope-to-intercept ratio can be observed to be further improved by adding urea.

For applications using gel dosimeters for quantitative analysis rather than proton range determination, properties of any formulation wishing to use glucose for improved sensitivity must be fully studied. For example, it has been reported that a gel with increased dose-R2 sensitivity often also suffers from increased sensitivity to dose rate and fractionation effects, as well as increased sensitivity to variations in manufacturing and handling of the gel.^{22,23} In our study, we repeated (A), the original MAGIC gel, three times and (D), MAGIC gel with glucose, twice. The variation in dose-R2 slope was 31.4% for (A) and 21.9% for (D). Also, for proton or other high linear energy transfer irradiations using gel dosimeters for quantitative dosimetry studies rather than range determination, it should be noted that a 20% under-response has been reported at the Bragg peak.²⁴ Although this will not significantly affect the range verification in our application, its effects must be fully investigated for quantitative dosimetry studies.

V. CONCLUSION

We have added glucose and urea to adjust the elemental compositions of the MAGIC gel dosimeter. The new gel has very similar time-activity response compared to soft tissue for PET verification of proton therapy, and therefore is a preferable material for this type of application. In addition to improved tissue equivalency, specifically the O/C ratio, we found that the sensitivity of the gel was substantially improved by glucose, especially the slope of the dose response curve. The improvement was slightly reversed by adding urea because of increased R2 intercept with MRI measurements, but could be a further improvement if optical CT is used for gel readout.

ACKNOWLEDGMENTS

Dr. Lee Josephson of MGH Department of Radiology provided valuable insights into the role of glucose in the gel system. This work was supported by NIH Grant Nos. R21-CA134812 and T32-EB002102.

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FIG. 2. Expected time-activity response curves of PMMA, the original, and modified MAGIC gels, and soft tissue. The responses of the modified gels are very similar to that of soft tissue at all time frames. PMMA has lower response at the beginning and higher response at later time frames. The original MAGIC gel has lower response at later time frames.

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