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Invited Article

Effect of D-(+)-Glucose on the Stability of Polyvinyl Alcohol Fricke Hydrogel Three-Dimensional Dosimeter for Radiotherapy

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ABSTRACT

D-(+)-glucose (Glc) was added to the original Fricke polyvinyl alcohol–glutaraldehyde –xylenol orange (FPGX) hydrogel dosimeter system to make a more stable FPGX hydrogel three-dimensional dosimeter in this paper. Polyvinyl alcohol was used as a substrate, which was combined with Fricke solution. Various concentrations of Glc were tested with linear relevant fitting for optimal hydrogel production conditions. The effects of various formulations on the stability and sensitivity of dosimeters were evaluated. The results indicated that D-(+)-Glc, as a free radical scavenger, had a great effect on stabilizing the dose response related to absorbency and reducing the auto-oxidization of ferrous ions. A careful doping with Glc could slow down the color change of the dosimeter before and after radiation without any effect on the sensitivity of the dosimeter.

1. Introduction

The Fricke solution was firstly used as a kind of dosimeter for radiotherapy in the 1980s because of its good sensitivity to radiation including x-rays and gamma rays. The ferrous ions (Fe^{2+}) in Fricke solution turn into ferric ions (Fe^{3+}) [1] by oxidization under ionizing radiation, and the change from Fe^{2+} to Fe^{3+} can be investigated with UV–visible spectroscopy [2]. In order to stabilize the dose distribution of a Fricke solution dosimeter, the Fricke solution is incorporated into a gel matrix so that the dose distribution can be measured in three dimensions using magnetic resonance imaging or optical computed tomography [3]. With the development of three-dimensional dosimeters, stabilizing the geometric dose information by incorporating the aqueous Fricke solution into a gel and adding additives have become two important aspects for improving the stability and the sensitivity of the dosimeters.

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A number of gel systems have been used as the substrate of gel dosimeters. Among these, agarose [1] and gelatin [4] are the popular choices, but they have disadvantages in preparation and transparency which limit their application in Fricke gel dosimeters. Recently, polyvinyl alcohol (PVA), considered as a tissue-equivalent gel system, has been reported in use as a gel matrix [5]. As a common water-soluble polymer, PVA is often used in the film and adhesive industries. Compared with other organic gel materials, it has advantages such as being obtainable with tight manufacturing tolerances, low impurity levels, nontoxicity, and it can be prepared in the presence of oxygen. Besides, when mixed with Fricke solution, a PVA-made gel matrix can be analyzed by either optical computed tomography or magnetic resonance imaging detection methods because of its good transparency and stable performance.

In order to improve the stability of the dimensional dose information, some additives are used in Fricke gel dosimetry and the most common one is xylenol orange (XO), a chelator that forms two or more coordination bonds with central ferrous or ferric ions. Ferrous ions bind to XO forming a colored complex (XO–Fe^{2+}) in the visible range which can be measured spectrophotometrically (Fig. 1) [6].

After adding XO into the system, the diffusion of the ferric ions become slow [reaction Eqs. (2–8) in Fig. 2] [7]. This is due to the formation of a complex which is much bulkier than the "free" ferric ions [8]. However, adding XO also alters the absorption spectra of the Fricke gels so that irradiated gels give visible color development [8]. We have already done immense amounts of research on Fricke PVA–glutaraldehyde (GA)–XO (FPGX) hydrogel dosimeters [9–12], in which the gel was cross linked by GA [reaction Eq. (1) in Fig. 2].

Although the FPGX gel dosimeter is inexpensive and easy to prepare, the auto-oxidation of ferrous ions is still a problem which might eventually affect the spatial dose information. During our research, we found that D-(+)-glucose (Glc) could not only act as a reducing agent to decrease the auto-oxidation of ferrous ions, but it could also be the chelator after being oxidized into D-gluconic acid [13–15]. The reaction equations are given [reaction Eqs. (9–12) in Fig. 2]. In this experiment, we attempted to study the stabilization and dose response of FPGX gel dosimeters by changing the concentration of Glc.

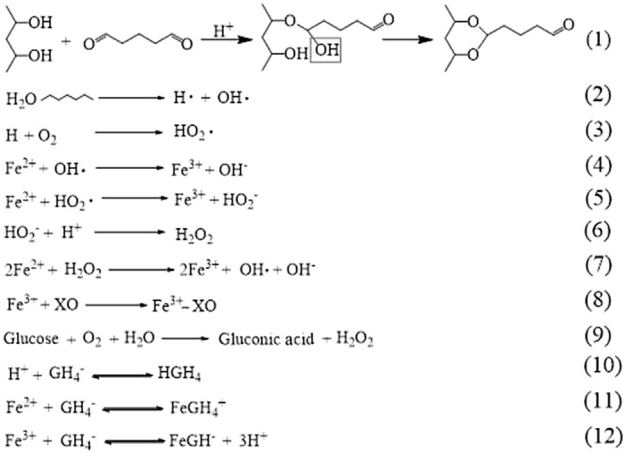

Fig. 2 – Reaction equations.

2. Materials and methods

2.1. Gel preparation

All chemicals used in this study were analytical grade and supplied by Sinopharm Chemical Reagent Co., Ltd (Shanghai, China). Ultrapure water from a Milli-Q Integral 5 water purification system was used in all preparation.

The basic hydrogel dosimeter formulation was according to our former experiment [9–12]. The mixture solutions with 30 mM sulfuric acid, 0.15 mM ammonium ferrous sulfate [$Fe(NH_4)_2(SO_4)_2 \cdot 6H_2O$], 0.015 mM XO, 0.025% weight/weight GA, 10% weight/weight PVA, and a series concentration of D-(+)-Glc (0 mM, 0.015 mM, 0.03 mM, 0.075 mM, 0.15 mM, 0.3 mM, 0.75 mM, and 1.5 mM) were prepared under nitrogen atmosphere. The prepared solutions were filled into the polystyrene cuvettes (10 mm, 10 mm, 45 mm), sealed with polytetrafluoroethylene caps, and kept in a dark place at 5°C for 10 hours. All experiments were repeated three times under the same conditions.

2.2. Irradiation experiments

Irradiation was performed by ^{60}Co with a dose rate of 0.3 Gy/min under 25°C (at Shanghai Institute of Measurement and

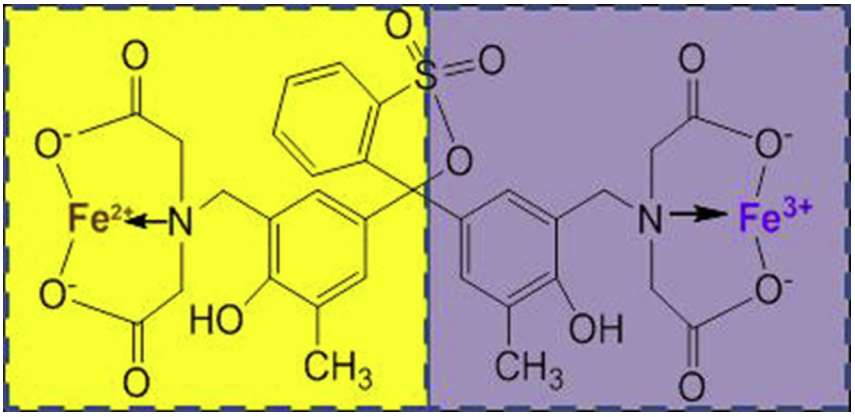

Fig. 1 – The reaction principle of xylenol orange and Fe^{2+}/Fe^{3+}.

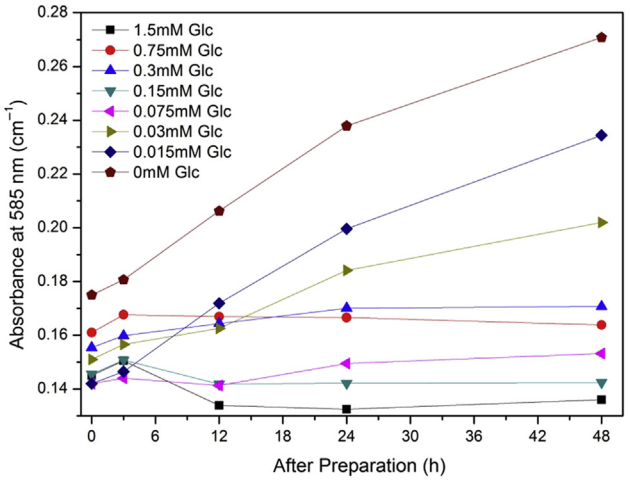

Fig. 3 – Stability of samples with different concentrations of glucose (Glc) before irradiation.

Testing Technology, Shanghai, China). Each formulation of the samples was irradiated by different doses (0.5 Gy, 1 Gy, 1.5 Gy, 2 Gy, 2.5 Gy, 3 Gy, 3.5 Gy, 4 Gy, 4.5 Gy, and 5 Gy), and one of each was left for the reference (0 Gy).

2.3. *Measurement of gel dosimeter*

The irradiated gels were stored at 5°C and scanned under room temperature (25°C) within 3–48 hours after irradiation. All the samples were scanned between 200 nm and 800 nm before and after irradiation using a UV–visible spectrophotometer (8453; Agilent, Santa Clara, CA, USA). All the data of the background absorbance, and changing absorbance before and after irradiation were determined based on the optical absorbance at 585 nm.

3. Discussion

3.1. *Effect of D-(+)-Glc on stability of gel dosimeters*

3.1.1. *Before irradiation*

Fig. 3 presents the changing absorbance of the gel dosimeters in all formulations during the 48 hours after preparation, and some differences could be seen between the samples. It is obvious to find that the absorbance of samples with Glc show better stability than those without Glc. Besides, the samples with 0.015 mM Glc and 0.03 mM Glc were less stable than other samples because the concentration of Glc was too low to stop the auto-oxidization. However, no obvious difference could be seen among different concentrations of Glc from 0.075 mM to 1.5 mM. Because Glc has an aldehyde group which showed reducibility in the system, it can reduce the rate of auto-oxidation of Fe^{2+} to keep it stable before irradiation.

3.1.2. *After irradiation*

For a better comparison of stability after irradiation between different formulations, Table 1 gives the linearity in terms of relative standard error (%). In general, the smaller the relative standard error is, the higher the stability of the hydrogel dosimeter. Because samples with 0.015 mM Glc and 0.03 mM Glc were less stable before irradiation, their results will not be discussed in this part. From these data we can clearly see that the formulations with Glc showed better stability than the samples without Glc. This phenomenon demonstrates that Glc had a great effect on the stability of gel dosimeters especially after irradiation because of its reducibility. Different from the stability before irradiation, the formulations with 0.075 mM Glc and 0.15 mM Glc showed better stability than the other formulations after irradiation. As mentioned before, after Glc was oxidized into gluconic acid, it became a good chelator to Fe^{2+} and Fe^{3+} [reaction Eqs. (9–12)] to slow down the next reactions, which indicates that the mole ratio of Fe^{2+} to Glc should be the key point to control the stability.

3.2. *Effect of D-(+)-Glc on dose response of gel dosimeters*

After being irradiated from 0 Gy to 5 Gy, each formulation has its linear regression equation $y = kx + b$ and linearly dependent coefficient (R^2). In the equation, k is the slope of the line, which means the sensitivity of the formulation and R^2 shows the ability of dose response. As shown in Table 2, adding Glc into the gel dosimeter has a complex effect on the sensitivity. When the concentration was 0.075 mM, k reached the peak. This demonstrates that Glc has a good influence on the sensitivity of the gel dosimeter. The reason is the reducing and chelating properties of Glc. With added Glc as a reducing agent, the auto-oxidation of Fe^{2+} was reduced, which helped to increase the sensitivity of the gel dosimeter. When the concentration of Glc was higher than 0.075 mM, the sensitivity decreased. Excess Glc reacted with Fe^{3+} which had already

Table 1 – Relative standard error of samples with different concentrations of glucose (Glc) after irradiation for 48 hours.

No.	Concentration of Glc (mM)	Relative standard error after irradiation (%)										
		0 Gy	0.5 Gy	1.0 Gy	1.5 Gy	2.0 Gy	2.5 Gy	3.0 Gy	3.5 Gy	4.0 Gy	4.5 Gy	5.0 Gy
1	1.500	1.032	1.224	1.288	1.405	1.490	1.617	1.599	1.642	1.583	1.435	1.563
2	0.750	0.975	1.106	1.067	1.364	1.379	0.962	1.334	1.023	1.004	0.823	1.152
3	0.300	0.984	0.658	0.958	0.849	1.137	0.995	0.973	0.820	0.769	0.766	0.917
4	0.150	0.932	0.616	0.882	0.778	0.432	0.601	0.842	0.375	0.701	0.516	0.899
5	0.075	0.768	0.697	0.904	0.688	0.750	0.330	0.659	0.660	0.665	0.195	0.812
6	0.000	3.777	1.637	1.684	1.413	1.741	1.816	2.054	2.416	1.835	1.758	1.743

Table 2 – The slope and R^2 of different concentrations of glucose (Glc).

No.	Concentration of Glc (mM)	Slope ($cm^{-1}Gy^{-1}$)	R^2
1	1.500	0.0607	0.9142
2	0.750	0.0590	0.9061
3	0.300	0.0716	0.9703
4	0.150	0.0769	0.9814
5	0.075	0.0923	0.9945
6	0.000	0.0583	0.8580

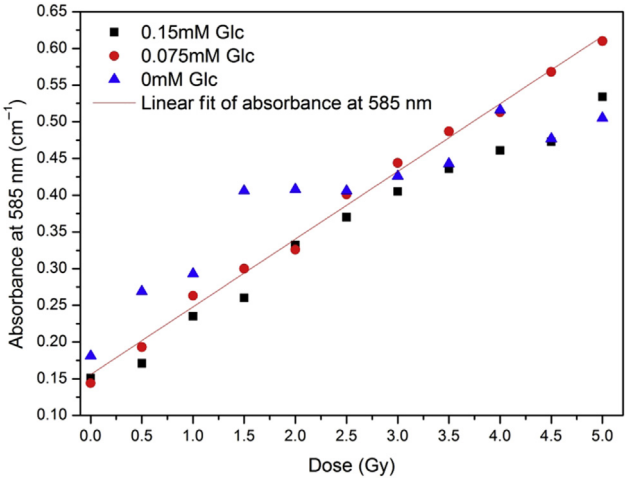

Fig. 4 – The dose-response curve of different dosimeter systems after irradiation for 3 hours. Glc, glucose.

been oxidized by the oxidizing species HO_2•, •OH, and H_2O_2 formed in the water of the irradiated solution. Too much Glc will chelate Fe^{2+} and stop the oxidation reaction caused by irradiation. Besides, it will also chelate Fe^{3+}, so that XO will combine with less Fe^{3+}. All these factors will slow down the color change of dosimeters after irradiation, which will cause a sensitivity decrease of the hydrogel dosimeter. Added Glc has less of an effect on the dose response than it does on k, but they have the same changing trend. As mentioned before, excess Glc will disturb a series of reaction of Fe^{2+} and Fe^{3+}, which reduces the dose response of dosimeters. A comparison of no Glc, 0.075 mM Glc, and 0.15 mM Glc in dose response is shown in Fig. 4. Although the formulation of added 0.15 mM Glc showed good stability before and after irradiation, it was less sensible than the formulation of added 0.075 mM Glc. Therefore, 0.075 mM Glc would be the suitable concentration and the changing color of samples with 0.075 mM Glc after irradiation from 0 Gy to 5 Gy is shown in Fig. 5.

Fig. 5 – The samples after irradiation for 3 hours (30 mM H_2SO_4, 0.15 mM $Fe(NH_4)_2(SO_4)_2{\cdot}6H_2O$, 0.015 mM xylenol orange, and 0.025% glutaraldehyde, 0.075 mM glucose).

4. Conclusion

An FPGX gel dosimeter with good stability and sensitivity was obtained by adding Glc. The results showed that the Glc enhanced the stability but decreased the sensitivity with increasing concentration. In order to improve the stability of dosimeters and at the same time keep the sensitivity, the suitable concentration of Glc is 0.075 mM. Using this formulation, we finally found the linear regression equation, in which the slope of the line reached 0.0923 and the R^2 reached 0.9945.

Conflicts of interest

The authors have nothing to disclose.

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