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A study on Fricke-PVA-xylenol orange hydrogel dosimeter for E-beam radiotherapy

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Abstract A Fricke-PVA-xylenol orange (FPX) hydrogel dosimeter, in good transparency, was prepared by physical crosslinking for three-dimensional dose measurements. The process of mixing the chemical dosimeter with the PVA solution was carried out at room temperature, which reduced the influence of auto-oxidation rate. Gradation in color was obviously observed with different distance from the radiation source after 6 MeV electron beam irradiation for radiotherapy. The effects of irradiation dose and three components of the FPX gel dosimeter, i.e. ferrous ions, xylenol orange (XO) and sulphuric acid on sensitivity and stability of dose response were investigated by UV-vis spectrophotometric measurement. The dose response of the FPX gel dosimeter was linear in the range 0~2.0 Gy. The orthogonal test was employed to find the optimal composition of the gel dosimeter with a sensitivity of about 0.095 $cm^{-1}\cdot Gy^{-1}$. It was found that XO concentration greatly affected the sensitivity of dose response and lower concentrations of the ferrous ion and XO gave higher sensitivity within the range 0~2.0 Gy.

Key words Fricke-PVA-xylenol orange (FPX), Hydrogel dosimeter, Radiotherapy, Electron-beam

1 Introduction

The traditional gel dosimetry method has been widely used in radiotherapy [1,2]. The dose distribution measurement is based on gel-layer dosimeters and Monte Carlo (MC) simulations [3,4]. Because the method is not capable of giving 3D dose distribution in the irradiated volume, polymer gel dosimeter simulating the body tissue has been developed.

Conventional polymer gel dosimeters are composed of water-based gelatin in which monomers are dissolved, such as BANG polymer dosimeters [5-7]. However, the gel dosimeters must be prepared under hypoxic condition. Otherwise, the radiation-induced polymerization would be inhibited by oxygen. Also, some monomers are toxic. As an alternative, Fricke-gelatin-xylenol orange (FGX) gel dosimeter, simpler and safer, was developed [8-10]. It consists of ferrous ions in the acid environment with the metal ion indicator xylenol orange(XO). The orange color changes into purple, when the gel dosimeter is exposed to ionizing radiations, and the ferrous ions (Fe^{2+}) are oxidized to ferric ions (Fe^{3+}), which combine with XO to form XO-Fe^{3+} [11]. The mechanisms of reactions are as follows:

$$H_2O \rightsquigarrow H\cdot, OH\cdot, H_2O_2, H_2, e^-_{aq}$$
$$Fe^{2+} + OH\cdot \rightarrow Fe^{3+} + OH^-$$
$$e^-_{aq} + H^+ \rightarrow H\cdot$$
$$H\cdot + O_2 \rightarrow HO_2\cdot$$
$$Fe^{2+} + HO_2\cdot \rightarrow Fe^{3+} + HO_2^-$$
$$HO_2^- + H^+ \rightarrow H_2O_2$$
$$2Fe^{2+} + H_2O_2 \rightarrow 2Fe^{3+} + 2OH^-$$
$$Fe^{3+} + XO \rightarrow XO\text{-}Fe^{3+}$$

The radiation-induced color change enables optical analysis to measure spatial dose distribution, and the optical analysis technique is used as a simpler and

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less costly alternative to magnetic resonance imaging (MRI) [9.10,12,13].

In this work, polyvinyl alcohol (PVA) was used as the gelling agent of the dosimeter. As a water-soluble, non-toxic and biocompatible polymer, PVA has been widely applied in biomedicine [14]. PVA-Fricke gel dosimeter shows a lower Fe^{3+} diffusion coefficient of 0.14 $mm^2 \cdot h^{-1}$(at 20ºC) than similar preparations reported for gelatin or agarose [15,16]. Alternatively, the diffusion coefficient can be lowered by using chelating agent [17], such as XO, which was used to anchor the Fe^{3+} ions for this study. Prepared by freezing and thawing the mixture of the PVA solution and the chemical dosimeter, the hydrogels were in good transparency. This could increase the sensitivity of dose response. After irradiation on a medical linac, a visible color change was shown as a function of absorbed dose, and dose distribution of the target regions could be easily determined. Effects of the three components of the dosimeter on the sensitivity of dose response were studied to optimize the composition. Lower additive amount of ferrous ions and xylenol orange gave better sensitivity in the 0~2.0 Gy range. Self-oxidation stability of the dosimeter post- irradiation was investigated so that the practical recommendations on the storage and usage could be made.

2 Materials and methods

2.1 Materials

PVA-124 was purchased from Sinopharm Chemical Reagent Co., Ltd and used without any treatment. Ferrous sulphate heptahydrate ($FeSO_4 \cdot 7H_2O$), sulphuric acid (H_2SO_4) 98% and XO are analytical reagent and used without any purification.

2.2 Preparation of FPX system

PVA powder and ultrapure water from Onwater GT-8 water purifier were mixed together and heated at approximately 90ºC to form a clear aqueous solution of 10% (w/w). The PVA solution was allowed to cool to room temperature. For the chemical dosimeter, a solution mixture was prepared by dissolving successively H_2SO_4, $FeSO_4 \cdot 7H_2O$ and XO within a small enough amount of ultrapure water. The light-orange FPX dosimeter solution was obtained by uniformly mixing the chemical dosimeter with the PVA solution. The mixture was allowed to defoam at room temperature in dark for a while, before it was filled into the 4.5 mL optical cuvettes (10-mm long) and frozen at –20ºC for 1~1.5 h to form stable hydrogels. They thawed into transparent gel dosimeters at room temperature.

2.3 Irradiation of gel dosimeters

The FPX gel dosimeters were irradiated on a medical linac (Synergy® IGRT, Elekta, Sweden) at 6 MeV. According to dose requirement of radiotherapy, the irradiation doses were 0.5, 1.0, 1.5 and 2.0 Gy. After irradiation, the gel dosimeters became purple in degrees related to the doses. The gel samples were stored at 3ºC before irradiation, and could be used several days after preparation.

2.4 Optical measurements

The change of optical absorbance before and after irradiation was evaluated by using a UV-vis spectrophotometer (8453, Agilent, USA) at 585 nm, which is the maximum absorption peak of XO-Fe^{3+} complex. The optical measurements were conducted at 25ºC a few hours after irradiation and repeated in later hours and days.

3 Results and discussion

3.1 Dose response

The 0.5~2.0-Gy irradiation is within the dose limit for one irradiation of a treatment. Fig. 1 shows that the absorbance around 585 nm increases in proportion to the dose up to 2.0 Gy.

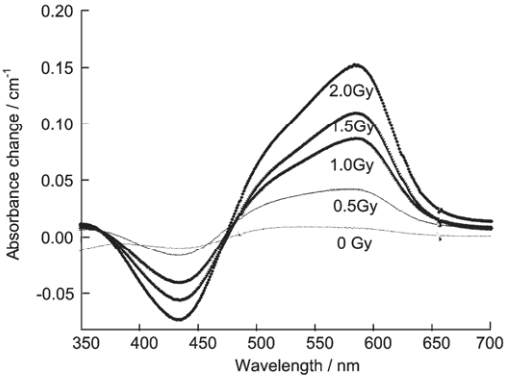

Fig. 1 UV-vis spectra of the FPX gel dosimeter with XO, 0.0165 mmol/L; $FeSO_4 \cdot 7H_2O$,0.05 mmol/L; H_2SO_4, 25 mmol/L; and PVA,10% (w/w).

The 585-nm absorbance change of the irradiated FPX gel dosimeter increased linearly with the dose from 0 to 2.0 Gy (Fig. 2). The slope shows a sensitivity of 0.07443 $cm^{-1}\cdot Gy^{-1}$ at 585 nm. The intercept is about 0.007 cm^{-1}. This is because of the auto-oxidation of Fe^{2+} to Fe^{3+}, which increases the concentration of the complex XO-Fe^{3+} and leads the absorbance change at 585 nm.

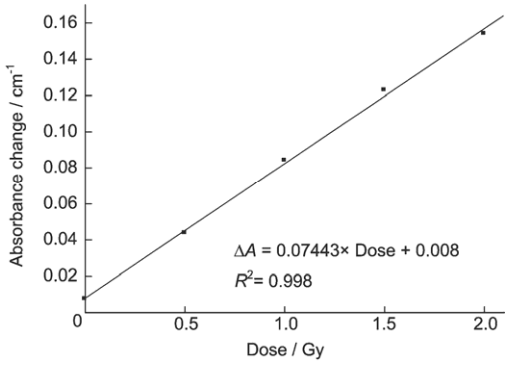

Fig. 2 Dose response curve of FPX gel dosimeter.

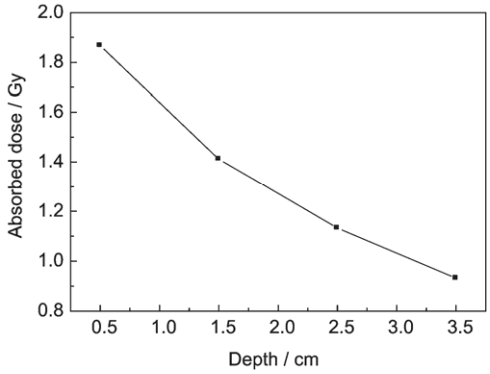

Fig. 3 Absorbed radiation dose as a function of distance from the surface of the gel dosimeter. The reagent concentrations were XO, 0.01 mmol/L; $FeSO_4\cdot 7H_2O$, 0.05 mmol/L; and H_2SO_4, 10 mmol/L.

The FPX gel dosimeter changes in color from yellow to light-purple after irradiation. And the color paled with the distance from the radiation source, which is related to the absorbed dose. Fig. 3 shows the absorbed dose as a function of distance from the gel dosimeter.

3.2 Composition effect on sensitivity and stability of the dose response

The samples were irradiated to 1.0 Gy to study effects of the three main components on the sensitivity and stability of dose response, and to find an optimal composition, by varying the concentrations of one reagent each time.

The effect of ferrous ions on the dose sensitivity is shown in Fig. 4. The sensitivity was the highest at 0.05 mmol/L of ferrous ion concentration, and decreased sharply at higher concentrations. This may be due to the interference of excess ferrous ions with the formation of XO-Fe^{3+} complex at low XO concentration (0.0165 mmol/L) and low dose (1.0 Gy). The dose response increased steadily in concentrations of 0.2~1.0 mmol/L. This may be the result of self-oxidation of ferrous ions, which has a greater effect at higher concentrations because the rate of this process is proportional to the square of ferrous ion concentration. The post-irradiation stability, i.e. the rate of absorbance change per unit dose ($cm^{-1}\cdot Gy^{-1}\cdot h^{-1}$), as shown in Fig.4, is relatively good 42 h after irradiation, but reduces with time, especially at higher Fe^{2+} concentrations.

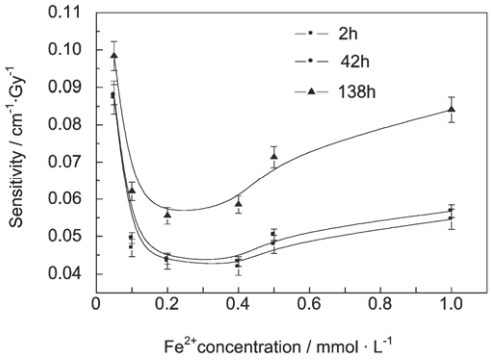

Fig. 4 Sensitivity *vs*. ferrous ions concentration. XO, 0.0165mmol/L; H_2SO_4, 25 mmol/L; PVA, 10% (w/w).

The effect of XO concentration on the sensitivity is shown in Fig. 5. The XO concentration affected just the dose sensitivity, but not the stability. The dose response was the most sensitive at around 0.015mmol/L. Slight changes of the sensitivity could be seen in 0.045~0.105 mmol/L of the XO concentration, which is much higher than Fe^{3+} concentration. This is because that the extra XO cannot bind with Fe^{3+} to form new complex. The gel dosimeter is relatively stable in no more than two days after irradiation. This is due to the auto-oxidation of ferrous ions, too.

Fig. 6 shows the effect of H_2SO_4 concentration on the sensitivity and stability. The H_2SO_4 content has a great effect on the dose response. At lower H_2SO_4 concentrations, the gels became less stable, and the concentration of XO-Fe^{3+} complex increased slowly even before irradiation. This indicates that the self-oxidation of ferrous ions is more likely to occur with less acid. At high concentrations, the dose sensitivity

falls off remarkably, as the acid inhibits the production of free radicals by radiolysis reaction of water in the gel and then the oxidation of Fe^{2+} to Fe^{3+} initiated by the free radicals.

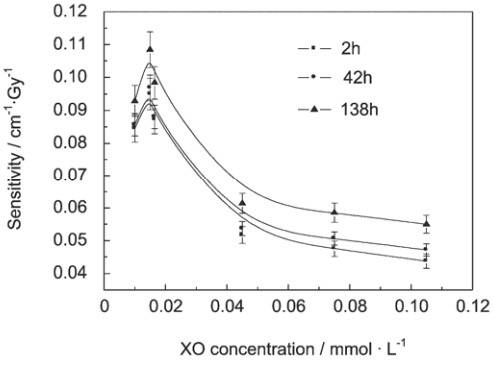

Fig. 5 Sensitivity *vs.* XO concentration. Fe^{2+}, 0.05 mmol/L; H_2SO_4, 25 mmol/L; PVA, 10% (w/w).

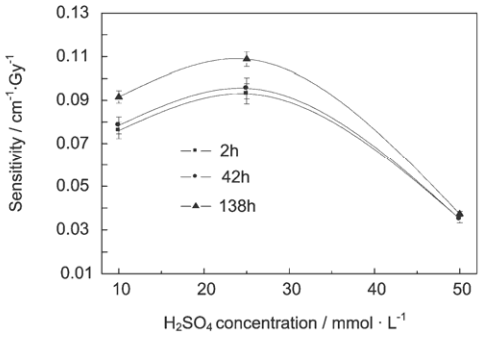

Fig. 6 Sensitivity *vs.* H_2SO_4 concentration. XO, 0.0165mmol/L; Fe^{2+}, 0.05 mmol/L; PVA, 10% (w/w).

3.3 Orthogonal test design

The composition effect on the sensitivity and stability was studied by varying the concentration of one reagent each time. However, the gel components would interact with each other. So a $L_{25}(5^6)$ orthogonal test was implemented to investigate the interactions and find the most important factor affecting the dose sensitivity.

The concentrations of the XO, $FeSO_4·7H_2O$ and H_2SO_4 were chosen as the factors, and the dose sensitivity as the reference index. Table 1, 2 and 3 show the factor and level of the orthogonal test, the results of range extremity difference analysis and variance analysis. The optical measurements of these samples were carried out 2 h after irradiation.

Table 1 The factor and level of orthogonal test (mmol/L)

Factor	Level				
	1	2	3	4	5
XO	0.01	0.015	0.02	0.025	0.03
$FeSO_4·7H_2O$	0.05	0.1	0.2	0.3	0.5
H_2SO_4	10	20	25	30	40

Table 2 The orthogonal test results and range extremity difference analysis

No.	XO	$FeSO_4·7H_2O$	H_2SO_4	Sensitivity/0.1cm^{-1}·Gy^{-1}	No.	XO	$FeSO_4·7H_2O$	H_2SO_4	Sensitivity/0.1 cm^{-1}·Gy^{-1}
1	1	1	1	0.8040	17	4	2	5	0.4407
2	1	2	2	0.7950	18	4	3	1	0.4890
3	1	3	3	0.7875	19	4	4	2	0.4965
4	1	4	4	0.6048	20	4	5	3	0.4416
5	1	5	5	0.6963	21	5	1	5	0.6123
6	2	1	2	0.9588	22	5	2	1	0.6444
7	2	2	3	0.9321	23	5	3	2	0.5526
8	2	3	4	0.9213	24	5	4	3	0.4845
9	2	4	5	0.9237	25	5	5	4	0.4983
10	2	5	1	0.9546	k1	0.738	0.691	0.735	—
11	3	1	3	0.6228	k2	0.938	0.693	0.697	—
12	3	2	4	0.6513	k3	0.666	0.668	0.654	—
13	3	3	5	0.5880	k4	0.465	0.659	0.626	—
14	3	4	1	0.7851	k5	0.558	0.655	0.652	—
15	3	5	2	0.6840	R	0.473	0.038	0.109	—
16	4	1	4	0.4548	—	—	—	—	—

Note: k_{ij} = sum of the data of Level i in Column j/5; R = range extremity difference, which indicates influence of the factors on the result. $R_j = \max\{k_{ij}\} - \min\{k_{ij}\}$; i = 1, 2, 3, 4 or 5, j = 1, 2 or 3.

Table 3 Results of variance analysis

Factor	Q	f	S^2	F	Significance test
XO	0.655	4	0.1638	29.328	Significant
$FeSO_4 \cdot 7H_2O$	0.006	4	0.0015	0.269	—
H_2SO_4	0.037	4	0.0093	1.657	—
Error	0.07	12	0.0058	—	—

Note: Q, the sum of squared deviations, $f_j = n–1$, n is the number of levels in Column j, $S^2_j = Q_j/f_j$, and $F_j = S^2_j/S^2_e$ ($S^2_e = Q_e/f_e$, e is short for error).

Table 3 shows that XO concentration has the greatest impact on the sensitivity, while the effect of ferrous ion concentration is not remarkable. The order of factors affecting the dose sensitivity is XO > H_2SO_4 > Fe^{2+}. Higher sensitivity is at XO concentration = 0.015 mmol/L (Table 2). It is known that the system is unstable at lower acid concentration and higher ferrous ion concentration as a result of auto-oxidation of Fe^{2+} to Fe^{3+}, so the gel containing 0.015 mmol/L XO, 0.5 mmol/L Fe^{2+} and 10 mmol/L H_2SO_4 cannot be used for practical application. The optimal recipe of the FPX gel dosimeter is 0.015 mmol/L XO, 0.05 mmol/L $FeSO_4 \cdot 7H_2O$ and 20 mmol/L H_2SO_4.

4 Conclusion

The FPX radiochromic hydrogel dosimeter was prepared by freezing and thawing method in this work. The radiation-induced change in color of the gel can be observed visibly from yellow to purple. Three-dimensional dose distribution can be determined by optical measurements using spectrophotometer. The relatively optimum gel composition that shows higher sensitivity of dose response has been found for radiotherapy application. It contains 0.05 mmol/L $FeSO_4 \cdot 7H_2O$, 0.015 mmol/L XO and 20 mmol/L H_2SO_4. The gel dosimeter has relatively good stability in at least two days after irradiation.

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