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Review of Fricke gel dosimeters

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Abstract. The innovation of adding a gel matrix to the traditional Fricke dosimeter to stabilize geometric information established the field of gel dosimetry for radiation therapy. A discussion of Fricke gels provides an overview of the issues that determine the dose response of all gel dosimeters in general. In this paper we review some of the features of Fricke systems to illustrate these issues and, in addition, to motivate renewed clinical interest in Fricke gels.

1. Introduction

The ferrous sulphate (Fricke) solution had been well used for radiation dosimetry for over 40 years [1,2] when Gore [3], in 1984, proposed combining the system with magnetic resonance imaging to make possible three-dimensional radiation dosimetry. An important aspect of this development was to stabilize the geometric dose information by incorporating the aqueous Fricke solution into a gel matrix. Modern gel dosimetry was born through the development of this Fricke-gel (the conventional term for ferrous sulphate doped gel).

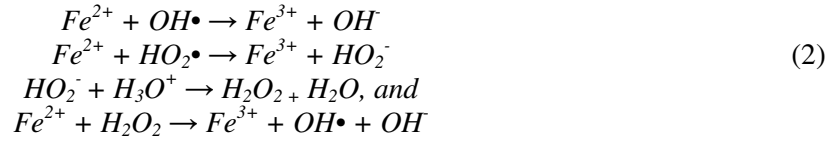
An understanding of Fricke gels is useful as it establishes characteristics common to all gel systems. For example, Fricke gels can be used to demonstrate the sensitivity of gel dosimeters to preparation conditions (chemical purity, additives, temperature, etc) and the relationship of dosimeter sensitivity to measurement parameters. On their own merit, Fricke gels have some advantages over other gel systems; for example, consistent reproducible Fricke gels are easily prepared and spatial dose determination is possible very soon after irradiation. On the other hand, Fricke gels have particular limitations not encountered with polymer gel dosimeters, such as time constraints between irradiation and measurement imposed by ion diffusion which eventually destroys the spatial dose information. Considering these points, the ferrous sulphate gel system still warrants consideration and discussion in this the third workshop on gel dosimetry. Furthermore, the development of new Fricke gel systems and innovations in optical techniques for probing dose all indicate a potential for the resurgence of Fricke based dosimeters. The purpose of this paper is to introduce the reader to these main aspects of the ferrous sulphate gel dosimeter.

2. Dosimetric basis for Fricke gels

The dosimetric basis of the Fricke solution (an acidic oxygenated aqueous solution of ferrous ion, Fe^{2+}) has been well established for decades: it is provided by the dose dependent transformation of ferrous (Fe^{2+}) ions into ferric (Fe^{3+}) ions [1,2]. When the solution is irradiated, water decomposition occurs and hydrogen atoms produced react with oxygen to produce the hydroperoxy radical:



Various reactions subsequently lead to the conversion of ferrous to ferric ions:



The quantity of Fe^{3+} produced depends on the energy absorbed by the solution. Specifically, the change in ferric ion concentration is related to the radiation dose (energy per unit mass) by [2]:

$$\Delta[Fe^{3+}] = \frac{D \cdot G(Fe^{3+}) \cdot 10\rho}{N_A \cdot e}, \quad (3)$$

where D is the dose, $G(Fe^{3+})$ is the chemical yield of Fe^{3+} (expressed in ions produced per 100 eV), ρ is the density in kg liter^{-1} , N_A is Avogadro's number and e is the number of Joules per electron volt. (Note here that I will follow the convention of most of the literature on Fricke solutions using the traditional chemical yield $G(Fe^{3+})$ rather than the G-value, or radiation yield, of ferric ions in mole J^{-1} .) The ferrous ion chemical yield for carefully prepared aqueous Fricke solution is 15.6 $\text{Fe}^{3+}/100 \text{ eV}$ [2]. We will note below that the ferrous ion chemical yield in Fricke gel systems is increased from this aqueous Fricke value because of the addition of chemical pathways for the conversion of Fe^{3+} provided by the gel macromolecules [4–6]. The basis for Fricke and Fricke-gel dosimetry stems from equation (3): the dose absorbed by an irradiated Fricke dosimeter can be determined by measurement of the concentration change of Fe^{3+} .

3. Gel composition and preparation

The required constituents for a typical Fricke gels are: triply distilled or well de-ionised water, ferrous ion (usually from ferrous ammonium sulphate), sulphuric acid, air or oxygen, and gel. The ferrous ion provides the chemical probe for the dosimeter while the gel provides some spatial localization of the radiation-induced changes. Typically the gel is added to 75% of the water and heated until the gel has dissolved. The other required chemicals are added to the remaining water, and this solution is mixed with the gel solution and the combination is kept at high temperature for a short period to ensure complete mixing. The dosimeter is then removed from heat so that the gel can set. Air or oxygen is bubbled through the solutions during the entire process to ensure that the dosimeter is well oxygenated, since oxygen is required for the radiation chemistry to proceed. Care must be taken during the bubbling after the solution is removed from heat, or the dosimeter may froth as it is setting and become nonuniform. After preparation, the solution is usually kept cool and in the dark to limit spontaneous oxidation (i.e., the spontaneous conversion of Fe^{2+} to Fe^{3+} which inevitably occurs). It can be noted here that the procedures and facilities for preparing reproducible Fricke gel dosimeters are

considerably simpler than required for most polymer based dosimeters (which contain toxic constituents and usually require anoxic conditions during preparation).

A number of different gel systems have been proposed for gel dosimetry, but agarose [4,5,7–11], and gelatin (usually 300 Bloom porcine) [6,8,12,13] are the usual gels of choice. Alternatives such as Sephadex and agar [14–16] have only seen limited use. Recently, a novel Fricke gel based on a polyvinyl alcohol (PVA) cryogel has been reported [17], this rubber-like gel is formed by the freezing and thawing of an aqueous PVA solution infused with Fricke solution and xlenol orange. The dose response of Fricke gels depends critically on the gel used in the preparation; this is reviewed further below. At this point we can note that agarose and gelatin both produce stable, well characterized dosimeters. Gelatin is somewhat easier to use as it dissolves in water at around 45°C, a lower temperatures than the 90°C required to dissolve agarose. This eases preparation and may provide more reproducible gels since oxygen removal from the gel solution is less at the lower temperature. Also, it has been suggested that the gel matrix in agarose may be degraded to a larger degree in the acidic solution because of the higher temperature of preparation [18].

It has been proposed from early in the development of Fricke gels that specific additives, or dopants, could be included in the gels, for example, to increase the dose sensitivity [7,19], to enhance uniformity of gel preparation [20], and to provide mechanisms to enable optical probing of ferric ion conversion [4,7]. Again, as discussed below, these additives alter the dose response of the Fricke gels.

One advantage of Fricke gel dosimeters is that they exhibit excellent water and tissue equivalence for dosimetry [21–23]. Therefore, correction factors converting Fricke gel measurements to dose in water or tissue are negligible. Calculations of density, electron density and attenuation coefficients [21,23] along with Monte Carlo simulations [22,23] all support this conclusion. There are some small differences in the attenuation coefficients and energy absorption coefficients with respect to water at photon energies below 100 keV, with the Fricke solution having coefficients up to 9% higher at these low energies. However, for a large range of energies of interest in radiation therapy, the Fricke gels are water equivalent (see figure 1).

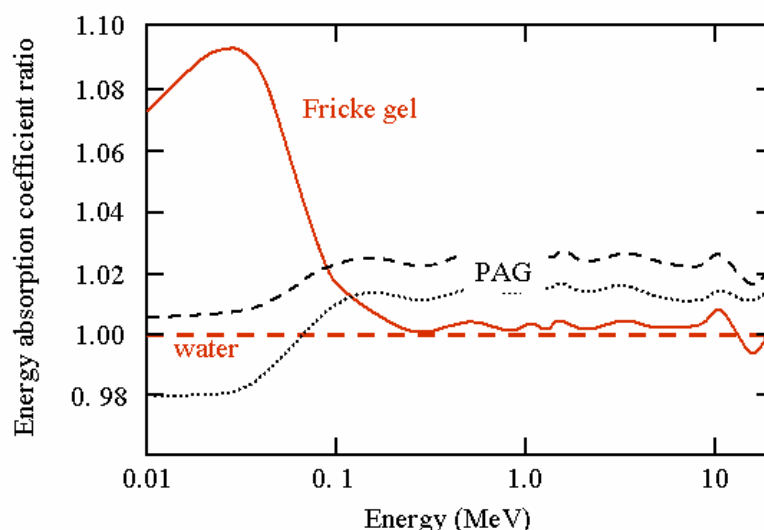


Figure 1. The results of Monte Carlo calculations comparing the energy absorption coefficients of Fricke gel (solid red curve) and two compositions of polyacrylamide gels (PAG; black dashed curves) relative to water. The top and bottom PAG curves are for the BANG (Bis acrylamide nitrogen gelatin) and initial BANANA (Bis acrylamide nitrous oxide and agarose) recipes for PAG [24,25] (modified from Keall and Baldock, [23]).

4. Dose measurement

From equation (3) it is clear that dose measurement with Fricke dosimeters depends on the reliable determination of the radiation induced change of the ferric ion concentration. The success of Fricke dosimetry over other chemical radiation measurement techniques was the ease and reliability of the Fe^{3+} concentration determination using spectrophotometry. This technique is based on the optical property of ferric ion, which absorbs strongly in the ultraviolet at 224 and 304 nm [3]. The dose of an irradiated ferrous sulphate solution is given by [2,26]:

$$D = \frac{N_A \cdot e}{\rho \cdot l \cdot G(\text{Fe}^{3+})} \cdot \frac{OD(D) - OD(0)}{\epsilon_m} \quad (4)$$

where l is the optical path length (width of the cuvette holding the solution), $OD(D)$ and $OD(0)$ are the optical densities at 304 nm of the irradiated and unirradiated dosimeter, respectively, and ϵ_m is the molar extinction coefficient for Fe^{3+} (a fundamental characteristic of the ion $\sim 2200 \text{ M}^{-1}\text{cm}^{-1}$ at 25°C for aqueous Fricke solution [7,26]); the other symbols are as in equation (3). Equation (4) retains the same form for optical dose probing with Fricke gel dosimeters and with optical computed tomography CT scanning systems.

In 1984, Gore *et al* [3] proposed that the radiation induced changes in the Fricke dosimeter could also be probed with nuclear magnetic resonance (NMR) relaxation measurements. The NMR relaxation behaviour of the Fricke system is dependent on the concentration of the ferrous and ferric ion species, since the solution's observed spin-lattice relaxation rate ($R_1 = 1/T_1$) is dominated by the dipolar interaction between the paramagnetic spins of the ions and the adjacent water protons [3]. The Fe^{2+} and Fe^{3+} ions possess different paramagnetic characteristics and, hence, perturb the relaxation of neighboring water protons differently [3,6,18,27]. Thus, since the concentration of the ions changes under irradiation, the observed NMR relaxation of irradiated Fricke solution is dose dependent.

The NMR relaxation in aqueous Fricke dosimeters is well described by a fast exchange model in which water is considered to exist in three environments (in the bulk and hydrating both ferrous and ferric ions). Then the dose dependent relaxation rate $R_1(D)$ is [6]:

$$R_1(D) = \left\{ \left(r_{eff}^{3+} - r^{2+} \right) \cdot G(\text{Fe}^{3+}) \cdot \frac{10 \rho}{e N_A} \right\} \cdot D + R_1(0) \quad (5)$$

where $R_1(0)$ is the relaxation rate of the unirradiated dosimeter, and r^{3+} and r^{2+} are the relaxation enhancement parameters for the ferrous and ferric ions, respectively; more correctly, these are termed the relaxivities of the two ions. The relaxivities of each of the iron species are well known [6,18,27]. In fact, in aqueous Fricke solution the relaxivities and chemical yields of ferric ion are well enough established that NMR Fricke dosimetry can be used as an absolute dosimeter without the requirement for calibration [27]. When the dosimeter is incorporated into a gel matrix the details of the relaxation model become somewhat more complex [6], but equation (5) still holds as the new spin environments (associated with the gel and the associated hydration water) are incorporated through the relaxation rate of the unirradiated dosimeter $R_1(0)$. It is interesting to note that the equation (5) for the observed relaxation of the irradiated Fricke gel can be rearranged to give an equation analogous to equation (4) for the spectrophotometric measurements:

$$D = \frac{N_A \cdot e}{10 \rho \cdot G(\text{Fe}^{3+})} \cdot \frac{R_1(D) - R_1(0)}{\left(r_{eff}^{3+} - r^{2+} \right)} \quad (6)$$

The relaxivity of ferrous ion r^{2+} in gel can be taken directly from measurements in aqueous solution. However, the relaxivity of the ferric ion is an effective relaxivity (hence the subscript *eff*) that must be determined for the gel system (e.g., gelatin) since the ferric ion hydration is affected by complexing [6,18]. That is, the addition of the gelatin perturbs the Fe^{3+} hydration, and hence, the basic NMR characteristics of the dosimeter and the NMR dose measurement.

Examples of the radiation induced changes of optical density and the NMR spin lattice relaxation in two different Fricke systems are shown in figure 2. As predicted by equations (4) to (6), there is an extensive dose range over which the measured radiation response of the NMR and optical measurements are linear. The slope of the response in the linear regime is conventionally called the dose sensitivity. In NMR relaxometry based gel dosimetry, the dose sensitivity is given in $\text{s}^{-1}\text{Gy}^{-1}$; in optical measurements the dose sensitivity is often specified in $\text{cm}^{-1}\text{Gy}^{-1}$. Note that radiation response saturates at higher doses and the linear increase of response with dose breaks down. This results from the depletion of initial finite amount of ferrous ion and oxygen in the irradiated solutions, and is common to all gel dosimeters.

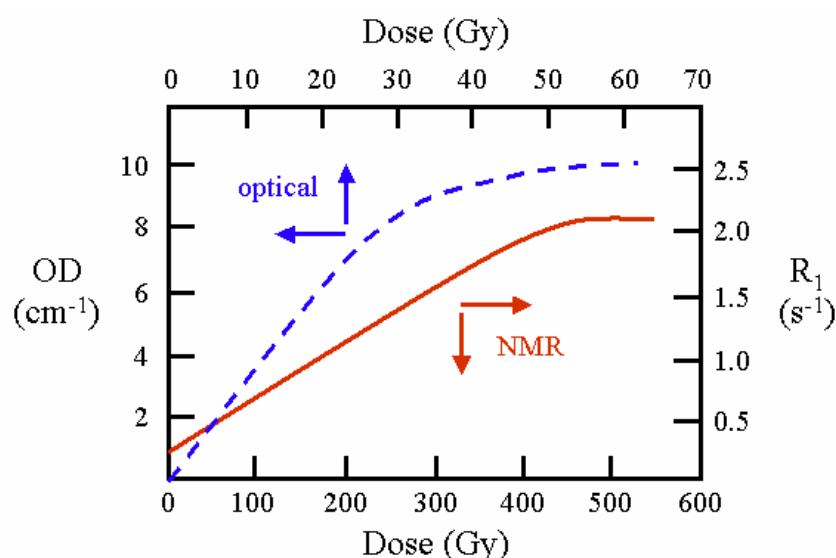


Figure 2. The dose dependent change in the optical density (in dashed blue) of a Ferrous sulphate xylenol orange dosimeter irradiated in the range from 0 to 70 Gy. The measurements were at 585 nm (from Bero [28]). The radiation induced change in the spin-lattice relaxation rate measured at 25 MHz (in solid red) of an aqueous Fricke solution irradiated from 0 to 600 Gy (from Podgorsak [27]).

The Fricke solutions require high doses for the radiation-induced changes to be readily observed by any probing technique; this is a drawback common to all chemical dosimeters. The aqueous Fricke solution requires tens of Gy for small changes in the relaxation rate and saturates at about 500 Gy [27]. This range is reduced considerably in Fricke gels with the linear region extending to about 50–75 Gy or so [6,9,12]. The increased sensitivity is seen also in ferrous sulphate xylenol orange dosimeters [28–30]. The dose required for measurable changes in Fricke gels is higher than required in current polymer gel dosimeters, which have higher dose sensitivity [24,25]. However, the doses required for reliable Fricke dosimetry are readily achieved in a reasonable time with clinical radiation therapy radiation units, and this is not a practical limitation except in very low dose rate applications.

Finally, the motivation for radiation measurement with gel dosimeters is that one can quickly obtain spatial dose information by imaging the radiation induced chemical changes using techniques sensitive to the physical changes discussed immediately above. The NMR relaxation characteristics can be probed via magnetic resonance imaging (MRI) [e.g., 10–15] while the optical changes can be measured using imaging of thin sections of gel [31–33], or by optical computed tomography (OCT) [30,34,35]. With these approaches, the imaging probes the differential concentration of Fe^{3+} throughout a phantom and can be analysed to give the spatial dose information. Such measurements are, of course, of most interest clinically in the assessment of conformal, i.e., non-uniform, dose delivery. Thus, in relevant clinical situations there are gradients, often very sharp, of Fe^{3+} in the phantom of interest. As a result of these gradients, there is diffusion of the ferrous and ferric ions even with the gel matrix added to the dosimeter to spatially stabilize the ion concentrations. Therefore, the spatial information is eventually destroyed [9,16,36–43]. Thus, in Fricke gel dosimetry there are practical, finite, time constraints from the start of irradiation to the end of the dose measurement. The diffusion of ions has been very well established and characterized by measurements of the iron ion diffusion coefficients. Not surprisingly, the diffusion coefficients of different preparations of Fricke gels are dependent on the type of gel, the gel concentration, the temperature and other properties of the dosimeter [36]. One can note here that it is the constraints imposed by diffusion on the practical time during which an irradiated Fricke gel can be imaged that was the main motivation for the development, and increased clinical use, of polymer gels [24,25].

5. Practical aspects of Fricke gel dosimetry

It has been noted a number of times in the discussion above that the dosimetric properties of Fricke gels are strongly dependent on the gel preparation (gel system, gel concentration, addition of other chemical components, temperature of preparation) and on the measurement conditions (time of measurement, NMR frequency, wavelength probed in optical measurements, etc). Therefore, it is vital that one characterize the particular implementation of Fricke gel dosimetry being established in the local setting (including the gel preparation protocols and the measurement conditions). We can illustrate the nature of these factors in this brief review by considering a few specific examples.

The chemical composition of the gel affects the radiation chemical yield (see table 1). In particular, organic impurities can introduce new pathways for Fe^{2+} oxidation [4,5,6,27], and the chemical yield increases. In fact, sodium chloride NaCl was specifically incorporated into the traditional aqueous Fricke [2] to help control the perturbation of the dose response by small amounts of organic impurity. This practice was carried over to the early preparations of Fricke gels, as shown in table 1 below, but this is likely not effective since the concentration of gel is so high [18,27,44]. One reported chemical yield of determination from NMR measurements of 183 $\text{Fe}^{3+}/100\text{eV}$ for agarose Fricke [11] is an overestimate because perturbation of the effective relaxivity of Fe^{3+} resulting from possible complexing was not considered in the calculation. Other additives or dopants, such as benzoic acid [19,30], have been included in the preparation of Fricke gels to increase the dose sensitivity [7,19]. The justification for such doping was based on an increase in the dose response of the doped Fricke gels relative to standard aqueous Fricke rather than to the response of undoped gels. More direct studies comparing the NMR response of Fricke gels with and without other additives show that the NMR dose response does not change significantly [11,18,44] with the incorporation of these agents in Fricke gelatin and Fricke agarose dosimeters. On the other hand, additives such as sugars can improve overall dose sensitivity in the Fricke xylenol orange dosimeters [20].

Table 1. Some typical recipes with concentrations of main constituents for the most common Fricke and Fricke gel dosimeters with representative chemical yields. References in square brackets.

Gel [reference]	[gel] (weight %)	[Fe ²⁺] (mM)	[H ₂ SO ₄] (mM)	[NaCl] (mM)	G(Fe ³⁺) (Fe ³⁺ /100eV)
Aqueous [27]	0	1	0.05	1	15.6
Gelatin [6,8]	4	1	0.05	1	45
	10				43
Agarose [5,8]	1	1	0.05	1	94
	1.5				
[13]	2				99
Polyvinyl alcohol [51]	20	0.4			~ 20
					38 (freeze thaw)

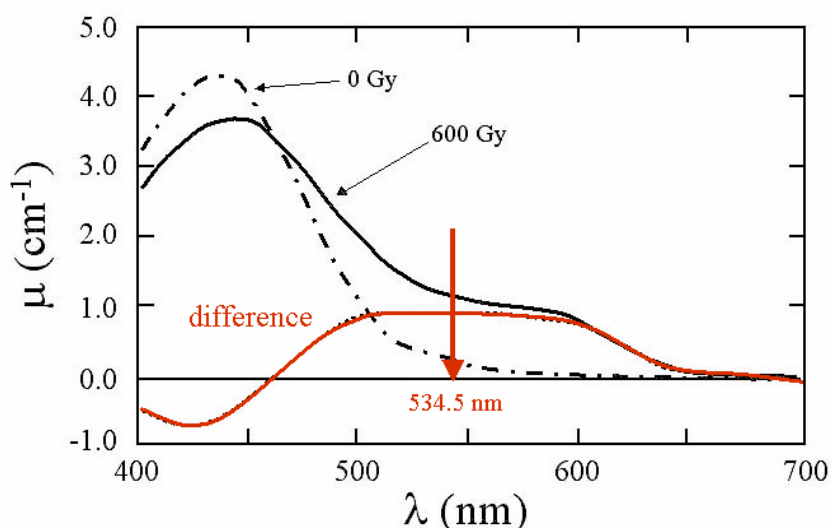


Figure 3. The change in the absorption spectrum of an irradiated ferrous sulphate benzoic acid xylene orange (FBX) dosimeter. The gel matrix was gelatin. The 0 Gy and 600 Gy spectra were measured with water as the reference. The difference spectrum (in solid red) has a broad peak centered at about 540 nm which is in the visible regime (from Kelly [30]).

Chelators, organic chemicals that form two or more coordination bonds with a central ferrous or ferric ion, are additives that seem to be well indicated for Fricke gel dosimetry. Appropriate chelators provide positive modifications for practical dosimetry: they improve the stability of the spatial dose information by reducing the diffusion coefficients of the iron ions [38] and they alter the absorption spectra of the Fricke gels so that irradiated gels give visible colour development [28–30,45–47] (see figure 3).

The reduction of ion diffusion is appealing since, as noted previously, the degradation of the spatial dose information resulting from ion diffusion provides the main limitation for Fricke gel dosimetry [36]. Chelating agents, such as xylene orange, significantly decrease diffusion, especially in gelatin Fricke dosimeters, as noted in table 2. To give some context to the problem of diffusion, we should consider instead of the diffusion coefficient, the time intervals over which dose distributions faithful to

the initial irradiation can be measured. Schulz calculates that an idealized heaviside gradient (with zero penumbra) will have an apparent 3 to 4 mm penumbra (90% to 10%) within 30 minutes [9]. However, others suggest that considerable dose distribution gradients (e.g., produced at the edges of blocked field, with pencil beam irradiations, or from single brachytherapy sources) can be well imaged with Fricke gels on the times scale of 1 to 2 hours [11,13,37]. Of course, the diffusion rate and its importance, will depend on the dose, and corresponding ion concentration, gradient [43]. As suggested by the diffusion coefficients summarized in table 2, the time available for dose measurement is greater in the Fricke chelator gels. Kelly [30] reports a time for the Fricke benzoic acid xlenol orange gelatin (FBX) system a factor 4 greater than that of conventional Fricke gelatin, particularly if the gel is cooled to 10°C. (Others have also reported on reduced diffusion at lower temperatures [16,38] but this can be inconvenient.) The spatial stability of a ferrous-agarose-xlenol orange gel (FAX) has been reported as 6 hours [29]. The new PVA xlenol orange cryogel Fricke dosimeter proposed by Chu *et al* [17] has a diffusion coefficient of $1.4 \times 10^{-3} \text{ cm}^2 \text{ h}^{-1}$, about one order of magnitude less than that of conventional Fricke gels and about half of that of the agarose and gelatin gels with chelator. Thus, with PVA gels one has about 10 hours in which to probe the dose distribution.

Table 2. An illustration of the changes in Fe^{3+} diffusion coefficients in Fricke gels doped with xlenol orange. Results are taken from measurements mainly at 20 or 22°C. Compiled from references [9,38,39,41].

gel	[gel] (w %)	Chelator and other additives	Diff. coef. ($10^{-3} \text{ cm}^2 \text{ h}^{-1}$)
Gelatin	4	None	8-14
		Xlenol orange	3-8
Agarose	1,1.5	None	13 – 20
		0.2 mM xlenol orange	10
		0.2 mM xlenol orange + sucrose	9.5
	3.0	None	16

A unique approach to controlling diffusion by adding a polyethylene honeycomb structure (with 5mm ‘voxels’) into the phantom containing agarose Fricke gel has been reported [48]. Profiles through MRI images of the phantom taken 2 hours and 24 hours after irradiation by a small square field were essentially identical. This approach may be quite useful, although it requires care to ensure the preparation of a uniform phantom, and it may not be amenable to optical imaging techniques.

As already noted, the addition of the chelator, xlenol orange, to gelatin, agarose or polyvinyl alcohol Fricke systems produces a dosimeter that can be probed using optical techniques. The development of optical techniques, particularly optical computed tomography, for gel dosimetry is a very active current research area and optical CT scanning is being developed for Fricke and polymer gel dosimeters [30,34,35,49,50]. The Fricke gels may present an advantage in this context as the light attenuation through the gel is determined by changes in the optical absorption coefficient of the irradiated gels whereas the differential attenuation in irradiated polymer gels is the result of increased scatter. Figures 3 and 4 illustrate that the difference spectra for the irradiated xlenol orange Fricke systems change significantly at, or close to, the wavelength of readily available green He-Ne lasers or xenon lamps [28–32]. The promise of optical techniques is that equipment specifically designed for Fricke-gel dosimetry can be established on-site in the clinic, removing the reliance on MR imagers, which are usually overburdened by diagnostic clinical demands. The availability of this on site imaging together with the increased time duration over which the xlenol orange Fricke gels retain the spatial dose information, is justifiably increasing the interest in Fricke gel for practical clinical dosimetry.

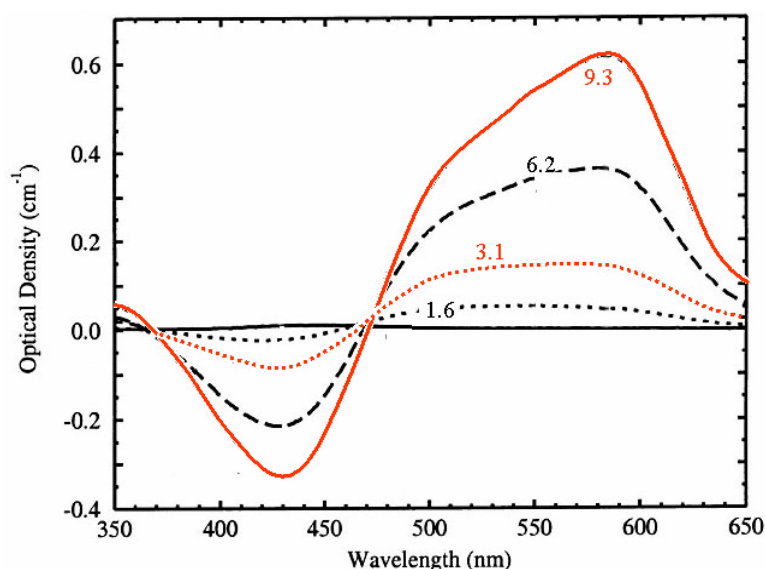


Figure 4: The change in the absorption spectra of irradiated Fricke xylene orange (FBX) dosimeter (without benzoic acid). The difference spectra (relative to an unirradiated dosimeter, as was illustrated in Figure 3) have spectra whose shape changes with dose. Note that if the absorption is measured at 440 nm the absorption decreases with dose whereas at 540 nm it increases. (From Bero, [28])

Before ending this introduction to the practical aspects of Fricke gel dosimetry we can consider a few brief points. There are other additional issues that determine the dose response of the Fricke systems. One can see from table 2 that diffusion also depends on the gel matrix and gel concentration in the Fricke dosimeter. The same is true of the dose sensitivity [28]. The addition of chelators, which improves diffusion characteristics of Fricke dosimeters, also affects the dose sensitivity [38,51]. This is the result of the modification of the chemical yield and, with NMR measurements, the perturbation of the Fe^{3+} relaxivity when encapsulated in the chelator molecule. The dose sensitivity will change depending on the concentration of chelator [17,38,51,53]. In both traditional Fricke gels and the new xylene orange dosimeters, the dose sensitivity also depends on factors such as initial Fe^{2+} and acid concentrations [20,51,52].

The response of the Fricke dosimeters depends also on other technical features of the dosimetry. The dose sensitivity depends on measurement properties such as NMR frequency [9,18,27] or optical wavelength [28,30]. The spontaneous oxidation of the gels depends on the gel preparation [20], which indicates that the time between the preparation and irradiation of the gels must be well defined. Subsequent to irradiation there is a short finite time (about 30 minutes) that must pass for the radiation induced reactions to stabilize [17,30,54] and the dose response to stabilize. The addition of saccharides to the Fricke xylene orange dosimeter also improves the uniformity of large gels, which can be influenced by temperature gradients across the gel during setting [20].

To finish on a positive point we can note that, in practice, the Fricke gel dosimeters are prepared in liquid form so that complex phantoms (e.g., containing heterogeneities mimicking lung or bone) can be produced [55–58]. The flexibility of Fricke gels to modification has been especially nicely indicated by the innovation of lung equivalent dosimeters prepared by adding Styrofoam spheres or by frothing with air as the gels set [57,58]. Polymer gels, which generally must be prepared in the absence of oxygen, have yet to exhibit such potential modification.

This discussion is not intended to be complete, rather it is intended to again emphasize that for reproducible Fricke dosimetry, one must take great care to characterize the particular dosimeter being used and to stick rigorously to preparation procedures when making the gels.

6. Conclusions

Fricke gel dosimeters have many attractive features. They are relatively easy to prepare without special facilities, are tissue equivalent over a very large photon energy range, and are readily probed by NMR and optical techniques very soon after irradiation. These advantages, together with the advent of techniques that enable one to probe the radiation dose more quickly, and the development of more stable Fricke systems, clearly indicate that Fricke gel dosimetry has a continuing role in radiation therapy in the clinic.

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Note: I have intentionally not referenced extensively the many articles compiled in the Proceedings of the 1st and 2nd International Workshops on Radiation Therapy Gel Dosimetry

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