Essential characteristics of polymer gel dosimeters

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Abstract. For a physical measurement instrument different requirements have to be fulfilled such as its insensitivity to uncontrollable environmental parameters and its stability. On the other hand, in order to meet an assigned accuracy, all measurement instruments should be operated in an approved manner. Polymer gel dosimeters are unique in their kind as they are able to integrate the dose in three dimensions and can be shaped in a humanoid form. In this paper, we focus on different characteristics that determine the accuracy of polymer gel dosimeters from the point-of-view of their use as 3D dosimeters in radiotherapy. It is shown that the accuracy is highly dependent on the composition of polymer gel. The comparison of the radiological characteristics may help in understanding the underlying mechanisms of the polymer gel dosimeters and in optimizing the chemical composition in terms of both dose and spatial accuracy.

1. Introduction

Essentially, polymer gel dosimeters consist of a hydrogel in which monomers are dissolved. Upon irradiation, a radiation induced polymerization reaction occurs. The degree of polymerization is dose-dependent. The polymer-structures that are created in the gel influence the mobility of the water molecules thus affecting the NMR spin-spin relaxation rate, R2 (= 1/T2). Dose maps from polymer gel dosimeters are reconstructed from R2 images by calibration with a dose-R2 curve obtained from a series of test tubes irradiated at various doses. Important to radiation dosimeters is the ability to measure absorbed dose with an acceptable precision and accuracy, independent of environmental factors and with a stable read-out. For three-dimensional dosimeters such as gel dosimeters the accuracy and stability is not only related to a measured dose value but also to the spatial integrity of the dose distribution. Therefore it is crucial that a set of dosimetric properties is verified. Since the development of the first polymer gel dosimeters, many gel compositions have been proposed as “potential” three-dimensional dosimeters but only a few of the essential properties have been tested thoroughly. Most of the properties have been determined for the polyacrylamide (PAG) gel with composition 3% acrylamide (AAm), 3% N,N’-methylene-bis-acrylamide (Bis), 6% gelatin and 88% water. A better understanding of the underlying chemical mechanisms that occur in polymer gel dosimeters may help in optimizing the chemical composition with respect to their radiation properties.
2. Chemical mechanisms of polymer gel dosimeters

A gel dosimeter is basically a hydrogel in which monomers are dissolved. The water content of gel dosimeters is generally in the order of 90%. To understand the physical mechanisms that take place in a gel dosimeter upon irradiation, we can rely to a large extent upon the physical processes that occur in water. Basic experimental observation is that for numerous solutions of different compounds in water the solute is not being affected directly by the radiation but indirectly by some entity or entities produced from water [1].

Upon irradiation, water molecules are dissociated in several highly-reactive radicals and ions [2,3] a process named “radiolysis”.

![Figure 1.](image)

Figure 1. Schematic drawing illustrating the creation of radiolytic products of water by ionizing irradiation. The radiolytic particles are created in spurs after which they diffuse and may react with other molecules (a). As a result, the interaction radius increases with time.

The cluster size of dissociated water products and the types of species that are created within the first femto-seconds are dependent on the type of irradiation (LET) and the energy. In the case of X-rays, gamma rays and electrons, the products occur in “spurs” (figure 1). These pre-thermal events occur in a time period of $10^{-15}$ s to $10^{-12}$ s. For 6 MV photons the location of the dissociated products is within 1 nm from the path of the incident ionizing particle. The observation of these events is limited by intrinsic quantum-uncertainties. From that moment onwards, the probability that these reactive particles reach each other by Brownian motion and react with one another in the form of chain reactions increases with time. As a result, the action radius starts to grow. After $10^{-11}$ s a local thermal equilibrium in the recombination of reactive particles is reached. With an average diffusion coefficient of the reactive particles of $4 \times 10^{-9}$ m$^2$.s$^{-1}$ in water [3] it can be estimated that after $10^{-11}$ s the quadratic average displacement of the particles from the point of creation is 0.28 nm which is only one tenth of the intermolecular distance of the monomers in a typical (PAG) gel dosimeter. As the molecular diffusion coefficient of water in the hydrogel is only 15% lower than in pure water [4] it can be expected that the diffusion coefficient for the radiolytic products of water is in the same order of magnitude.

After $10^{-8}$ s the quadratic average displacement amounts to 9 nm. The most present intermediates after $10^{-8}$ s are the aquatic electron, the hydroxyl radical (OH$^\cdot$) and the hydroxonium ion (H$_3$O$^+$).
These particles may react with the monomers. The hydrated electron, e\textsubscript{aq}—, reacts with the monomers by the formation of a radical anion that can be further neutralized by a proton [5].

In summary, the decomposition of reactive intermediates can be written as a simplified reaction of which the reaction rate is proportional to the absorbed dose.

\[ H_2O \rightarrow_{k_2} 2R^* \]  

The radicals initiate the polymerization of monomers by binding to an electron of the double bound of the monomer. The initiation step can be written as follows:

\[ R^* + M_n \rightarrow_{k_1(n)} RM_n^* \]  

Initially, there will be no polymers in the gel and \( n \) will be equal to one. However, as the cross-linking monomers have two double bonds on the same molecule, there can be reactive double bonds in the cross-linking polymer. Hence, during the complete period of polymerization there may be polymers \( M_n \) consisting of \( n \) monomer units that react with the radicals. Note the index \( n \) in equation (2). No quantitative data was found in the scientific literature on the reaction of polymers with the radicals. The reaction constant is dependant on the size of the polymers (i.e. the number of repetitive monomer units). It can be expected that the reaction rate will be smaller for larger polymers as the reactions are diffusion controlled [6] and the larger the molecule the larger the chance is that the reactive site on the molecule will be shielded [7,8]. This implies that the reaction rate \( k_1 \) can be seen as a function of the number of monomer units \( n \) [9]. Note that on the molecular level, it is not only the size of the polymer that is determining the reaction rate but also the shape of the molecule and the location of the reactive groups (double bonds) on the polymer. However, on a macroscopic scale one may think of a statistical average of the different configurations of co-polymers.

The growth of polymer chains is a result of propagation chain reactions by which the created monomer and polymer radicals react further with other monomers or polymer chains.

\[ RM_n^* + M_m \rightarrow_{k_{p(n,m)}} RM_{n+m}^* \]  

The general case in which a polymer radical with \( n \) monomer units reacts with a polymer of length \( m \) is illustrated in equation (3). Termination of the polymerization reaction takes place by the combination of two radicals or by disproportionation. In addition to termination reactions, the growing polymer-radical may also terminate by transfer of the radical group to other molecules [10]. Typical chain transfer constants \( C_M = k_{\text{trans}}/k_P \) of radicals are of the order of \( 10^{-3} \) to \( 10^{-4} \) [11]. The radical site on \( M_n^* \) may undergo further reaction such as initiation of a new growing polymer chain. The chain transfer agent may be the growing polymer but also the gelatin biopolymer [10]. The decrease of polymerization rate with increasing gelatin concentration provides some evidence of gelatin moderating the polymerization, possibly through chain transfer reactions or through scavenging of initiating fragments by the gelatin molecules [12].
In the case that there is oxygen in the gel, peroxide-radicals are created. These peroxide-radicals will quickly react with other radicals leading to a termination. This explains the inhibition that may occur in the low dose region of polymer gel dosimeters. Oxygen can be removed from the gel system by purging the gel solution with inert gases such as nitrogen or argon gas [13]. Another way to remove oxygen is by use of an antioxidant [14,15].

At high conversions of monomers, the viscosity of a polymerizing system becomes very high. This hinders termination by mutual interaction of growing chains but has less effect on the propagation reaction (equation (3)) because diffusion of the small monomer molecules is not that much affected by the increased viscosity. As a result, the rate of polymerization shows an increase with high conversions [1]. This effect of auto-acceleration [9] is also called the gel effect or Trommsdorff effect. It has been reported that in systems in which the polymer precipitates from the solution by the creation of a heterogeneous gel system, the increase of viscosity takes place very rapidly even at low conversions [16]. This effect has also been illustrated through mathematical models of dispersion radical polymerization kinetics [9]. The auto-acceleration caused by a decrease in the termination rate is also responsible for the increasing size of the polymer aggregates with increasing dose as has been observed by optical turbidity spectra [17].

It is not clear yet if the non-linear response in the low-dose region (seen from 0 to 1 Gy) [4] of most gel systems is a reflection of this sudden change or if it is due to inhibitors (such as oxygen) in the gel. Note that although most of the dose-R2 plots of polymer gel dosimeters are fitted against a linear or mono-exponential fit, it can be seen that the dose response in the dose-R2 range up to 1 Gy is less than in the higher dose range.

With polymer gel dosimeters in which crosslinking copolymerization occurs (such as the acrylamide / N,N'-methylenebisacrylamide (AAm/Bis) system) the kinetic models become more complicated due to the differences in reactivity of the two comonomers [18,19] and the change in the reaction rate coefficients during the growth of the copolymer-network. The different reaction rate of the comonomers leads to a shift in the instantaneous relative comonomer concentration [20,21]. The reaction rate of the copolymer-structures is not only dependent on the number of monomer units but also on the crosslinking density and the shape of the polymer structures [22].

According to Baselga et al [21], in the crosslinking copolymerization of an AAm/Bis aqueous solution, three different reaction steps can be observed: a pregel step, gelation and postgel reactions. In the pregel step, the crosslinked polymer particles are richer in Bis for both statistical and chemical reasons. At the gel point, the rate of reaction increases for both comonomers but the increment is larger for AAm. During gelation, the pre-gel particles are joined by chains which are slightly richer in AAm than only according to the reactivity of both monomers. On the network formation during the post gel phase characterized by slow crosslinking, only some hypothesis have been formulated such as the retardation by shielding of the radical group by the copolymer chains [4,8] and reorganization of the polymer networks [18].

Some studies have been performed on PAG gels and aqueous solutions with different ratios of AAm and Bis. From FT Raman spectroscopy studies it is seen that the relative content of AAm and Bis has a significant influence on the consumption rate of both monomers [19]. This is translated in a difference in dose sensitivity of gels with different compositions. Previously, it was reported that the dose sensitivity of PAG gel dosimeters is maximum for equal amounts (in weight) of monomer (AAm) and crosslinker (Bis) [23]. This finding appeared to be independent of scanning temperature. It was also found that the saturation R2 (the R2 for very high doses) increases with increasing crosslinker fraction.

In the study performed by Maryanski et al, it has been assumed that the dependence of dose sensitivity on crosslinker fraction reflects two opposing tendencies: an increase in sensitivity with crosslinker content up to 50%C (%C is the relative content of crosslinker with respect to the total amount of comonomer in percentages of weight) due to greater NMR relaxivity of more crosslinked (rigid) polymer, whereas a decrease in sensitivity with increase in crosslinker content beyond 50%C may be caused by lower reactivity of the crosslinker (Bis). The latter explanation has been
contradicted by several studies using FT-Raman spectroscopy in which it was found that the consumption rate of the Bis crosslinker monomer is twice as large as the acrylamide monomer [18,19,24]. The difference in consumption rate of comonomers makes that the relative fraction of monomer upon crosslinker changes with dose. Thus the polymer structures created at small doses differ from the structures created at larger doses. It has been proposed that the change in viscosity by structures rich in AAm at one hand and the higher incidence of comonomer reacting with itself at high crosslinker (Bis) concentrations at the other hand explains the dose sensitivity versus crosslinker concentration [25]. These reactions have also been described in previous works on crosslinked polyacrylamide gels [7,8,20,26].

Although no hard evidence has been published, we assume that in the methacrylic acid gels the methacrylic acid polymer chains react with the gelatin in a process called “graft polymerization”. This assumption is based on the physical properties of polymer gel dosimeters irradiated to different doses such as the completely different characteristics of ultrasonic speed and elasticity modulus [27], the different characteristics of restricted molecular self-diffusion of the water molecules, the melting temperature of both gels, the chemical stability of the gels [15] and the dose-R2 response curves obtained for different irradiation temperatures.

3. Macroscopic response of polymer gel dosimeters

From the structural and chemical studies, it can be concluded that the extent of the resulting polymerization reaction is dose-dependent. In the gel dosimeters that were studied so far, the formation of polymers results in a change in the visual opacity due to the creation of polymer aggregates that scatter visible light [17]. The change in optical properties enables to scan the gel optically [28,29].

To understand the effect of radiation induced polymerization in the magnetic resonance relaxation rates $R_1 (=1/T_1)$ and $R_2 (=1/T_2)$, it is practical to consider different proton pools (i.e. ensembles of protons that can be considered as belonging to molecules that experience the same chemical environment).

Three major groups of proton pools can be considered in a polymer gel dosimeter [30]: (1) the proton pool of free and quasi-free protons (denoted as mobile, mob). These are the protons from free water molecules and monomers; (2) the proton pool of a growing poly-acrylamide network (poly) and of water molecules bound to the macromolecules and (3) the proton pool of the gelatin matrix (gela) and of the water molecules bound to the gelatin.

It can be noted that in order to study other phenomena in more detail, a subdivision of these proton pools can be considered as well. In a study of the chemical stability of polymer gel dosimeters the third pool is subdivided in two pools [4].

According to the theory of Bloembergen, Pound and Purcell (BPP-theory) [31], the spin-spin relaxation of the different proton pools is governed by the rate of molecular “tumbling” and Brownian motion of the molecules that contain these protons. This results in a change of the efficiency of dipolar coupling between neighboring protons and as a result in a change in the diphase rate of the spin-magnetic dipole moments. As this is directly correlated with the spin-spin relaxation, it can be expected that the relaxation rate of the proton pools is correlated with the mobility of the protons within these pools. The different proton pools are thus characterized by different relaxation rates.

If the lifetimes of protons in the various environments are long compared to the characteristic correlation times of the environments, each environment has intrinsic relaxation rates that are independent of the specific lifetime value ($R_{2\text{mob}}$, $R_{2\text{poly}}$, $R_{2\text{gela}}$). If, furthermore, the lifetimes are long compared to these relaxation times, the NMR signal is the same as the sum of the signals from isolated, non-exchanging environments. When this happens, the relaxation curves are multi-exponential of which the population fractions of the different pools is determined by the coefficients of the different exponential components. This is the slow exchange case. On the other hand, when
these lifetimes are short compared to the relaxation times but still long compared to the correlation times (the rapid exchange limit), the observed relaxation curve will be mono-exponential with a relaxation rate that is the weighted average of the relaxation rates of the different proton pools in the entire sample [32]:

$$R2 = f_{mob}R_{mob}^2 + f_{poly}R_{poly}^2 + f_{gela}R_{gela}^2$$  \( (4) \)

For the R2 measurements that have been performed on polymer gel dosimeters, the condition of fast exchange is fulfilled.

Before irradiation, the second proton pool is empty while the first proton pool is at its maximum. Upon irradiation, the second proton pool starts to grow at the cost of the first proton pool. As a result the relaxation rate will change proportional with the amount of converted monomer.

The mobility of monomers is relatively high and thus also the mobility of water molecules bound to the monomers by hydrogen bridges. However, upon irradiation of the gel dosimeters, the molecular mobility is significantly reduced. As the mobility of the bound water molecules is reduced, the spin-spin relaxation is more effective, which is observed by an increase in the spin-spin relaxation rate (R2). A comparison of the change in R2 of gel dosimeters consisting of different monomers suggests that the change in relaxation rate can not be explained by the BPP-theory solely. In table 1, the dose sensitivity of different gel dosimeters is listed.

From studies in which different water pools are selectively inverted [33], it is seen that cross-relaxation can occur between the different proton pools, for example between protons of the polymer with protons of mobile water [34,35]. The exchange of magnetization may occur by proton chemical exchange between bound water and free water and by magnetization transfer between non-exchangeable macromolecular protons and bound water. It has been shown that magnetization transfer can also be mediated by chemical exchange interactions [36]. It is shown that both chemical exchange and magnetization transfer are influenced by the pH of the system. As a result of the different interactions between the different proton pools, the relaxation rates of the different pools as they occur in equation (14) (R2_{mob}, R2_{poly}, R2_{gela}) are not only determined by the mobility of the molecules but also by the exchange rates of protons. As some monomers have acidic or alkaline functional groups, the overall R2 relaxation rate also depends on the pH of the gel [35].

From table 1 it can be seen that the dose sensitivity of the different monomers is influenced by the functional group. The functional group determines both the polymerization rate of the monomers (inversely proportional to the half-dose value D_{1/2}) and the efficiency of cross-relaxation. The hydroxyl and amino groups serve as hydrogen bonding sites [34]. The hydroxyl-group seems to be more efficient than the amino-group in the exchange of magnetization. However, it is seen that the reaction rate of acrylamide in the PAG gel is much higher than of acrylic acid. As a result, the dose sensitivity of both monomers is nearly the same but the dose-range of the acrylic acid gel is larger than for the acrylamide based gel. Although the alkyl-group (in MAC and HEMA) does not have a large influence on the cross-relaxation efficiency it alters the polymerization rate of the monomers significantly.

The magnetization transfer between different proton pools can be used directly to scan the polymer gel dosimeters [37].
Table 1. Dose sensitivity of different polymer gel dosimeters (data obtained from Lepage et al 2001).

| Monomer                     | $D_{1/2}$ [Gy] | R2-dose sensitivity [s$^{-1}$ Gy$^{-1}$] | R2$_{sat}$-R2$_{0}$ [s$^{-1}$ Gy$^{-1}$] | Functional group |
|-----------------------------|----------------|----------------------------------------|----------------------------------------|-----------------|
| Acrylamide (AAm)            | 5.5 (± 0.1)    | 0.331 (± 0.012)                         | 4.2 (± 0.4)                            | O                |
| Acrylic Acid (AAc)          | 31.2 (± 0.1)   | 0.358 (± 0.006)                         | 10.6 (± 0.4)                           | O — C — OH       |
| Methacrylic Acid (MAc)      | 12.5 (± 0.1)   | 1.193 (± 0.048)                         | 18.4 (± 0.4)                           | O — C — OH       |
| 1-Vinyl-2-Pyrrolidone (VP)  | 23.6 (± 0.1)   | 0.082 (± 0.004)                         | (13.7 (± 0.4))                         | N — O            |
| 2-Hydroxyethyl Acrylate (HEA)| 5.5 (± 0.1)    | 0.498 (± 0.003)                         | 4.2 (± 0.4)                            | O — C — OCH$_2$CH$_2$OH |
| 2-Hydroxyethyl Methacrylate (HEMA) | 41.6 (± 0.1) | 0.046 (± 0.002) | 4.9 (± 0.4) | O — C — OCH$_2$CH$_2$OH |

The structural changes that occur in the different polymer gel dosimeters upon irradiation will also affect other properties. Divergent characteristics have been observed for ultrasonic speed, elasticity modulus and attenuation of ultrasonic waves in PAG gels and MAGIC gels [27]. The change in mass density of polymer gel dosimeters upon irradiation makes that the attenuation of x-rays can be used to scan the gel dosimeters [38,39].
4. Essential criteria and characteristics of polymer gel dosimeters

Gel dosimeters are used as integrating dosimeters that are able to capture the dose in three dimensions. This potentially makes this type of dosimeter very suitable for the verification of complex dose distributions as they occur in clinical settings such as is the case in for example conformal radiotherapy and brachytherapy. However, to be considered as a reliable dosimeter, the dosimeter has to meet several criteria: (1) the dose response should be measurable, significant and well-defined, (2) the dose response has to be stable (i.e. should not change with time), (3) the integrity of the dose distribution should be preserved over a long time period, (4) the dose response should not be susceptible to many environmental factors that may vary during operation (during irradiation and scanning) such as temperature, pressure and light, and to atmospheric gasses (5) the dosimeter should be tissue equivalent for the kind of radiation it is used for, (6) the dependency of dose response on radiation energy should be as small as possible within the spectral range of used irradiation, (7) the dosimeter should operate in a dose range that can be easily obtained with the radiation unit.

A few different polymer gel dosimeters have been developed since their invention in 1993. The difference between the gel dosimeters lies in the fact that basically the gels have a different composition. Changes in compositions are mainly the use of different monomers and the addition of chemicals in order to decrease the susceptibility to oxygen. It has been shown that different gel compositions result in different characteristics with respect to the essential criteria mentioned above.

4.1. The dose response and operating dose range

The underlying mechanisms that cause a change in the NMR relaxation rates upon irradiation are described in the previous paragraph. The change in R2 versus absorbed dose for a PAG gel (6%T; 50%C) is shown in figure 2.

Figure 2. (a) Dose-R2 response curve of a PAG gel (6%T; 50%C). Note the bi-exponential course. (b) displays the low-dose region of figure (a) and illustrates a lower slope.

From figure 2, it can be seen that the dose-R2 response curve for the PAG gel dosimeter is not linear but is well described by a bi-exponential function. In figure 2b, the low dose region of the dose-R2 curve is shown. It is clear that the slope (dose-sensitivity) in this region is smaller than in the dose region between 1 and 10 Gy. In the dose region between 1 and 10 Gy, the dose-R2 curve can be well approximated by a linear plot.
The R2-dose sensitivity for other gel dosimeters is given in Table 1. From the monomers listed, the gel dosimeter with the highest R2 dose-sensitivity is methacrylic acid (1.193 s⁻¹.Gy⁻¹) and with the largest dose range is hydroxyl-ethyl methacrylate (D₁/₂ = 41.6 Gy). In clinical radiation dosimetry, dosimeters are most often used in a relative manner in the sense that the dosimeter is exposed to the same treatment as the patient but with a different total radiation dose. The dose distribution is then scaled proportionally to the same dose range as that from the treatment. As a result the maximum dose delivered to the polymer gel dosimeter can be chosen arbitrary. In practice, the maximum dose is chosen in such a way that the R2-dose range is used optimal. In that case, two criteria should be met: (1) the R2-dose range is linear and (2) no non-linear (spatially dependent) dose responses occur within the operating dose range. Remark that the first criteria is not stringent as a non-linear R2-dose response can be used to calibrate the R2 maps. However, in that case a loss of dose resolution is expected.

The ability to resolve doses with polymer gel dosimeters is determined by the dose resolution [40]. The dose resolution, written as \( D_P \), is defined as the minimal detectable dose difference within a given level of confidence, \( p \). The dose resolution is related to the standard deviation on dose \( \sigma_D \) by the equation

\[
D_P = k_p \sqrt{2} \sigma_D
\]  

For a 95% confidence level the dose resolution becomes \( D_P = 2.77 \sigma_D \).

The total dose delivered to the dosimeter is scaled to cover the active dose range of the dosimeter. In this context, it is preferable to use the concept of dose resolution relative to the operating dose range, here defined as relative dose resolution \( D_P^{\%} \) :

\[
D_P^{\%} = \frac{D_P}{(D_{\text{max}} - D_{\text{min}})} = \sqrt{2} k_p \left( \frac{\sigma_D}{D_{\text{max}} - D_{\text{min}}} \right)
\]  

The dose-R2 curve is used to calibrate the R2 map. The uncertainty on the dose value \( \sigma_{D^*} \), extracted from the linear dose-R2 plot with equation \( R2 = R2_0 + \alpha \cdot D \), is given by

\[
\sigma_{D^*} = \frac{\sigma_c}{\alpha} \cdot \sqrt{\frac{(D^* - \bar{D})^2}{N_{\text{cal}}} + \frac{1}{N_{\text{cal}}}}
\]  

with \( \sigma_c \) the standard deviation on R2 in the calibration points [41]. This value is derived from the standard deviation in a region of interest of the calibration vials \( \sigma_{ROI} \). If \( N_{\text{ROI}} \) is the number of points in the region of interest, the standard deviation on the calibration point is given by

\[
\sigma_c = \sigma_{ROI} \sqrt{N_{\text{ROI}}} \cdot D^* \text{ is the estimated dose, } \bar{D} \text{ is the mean dose of all dose values in the calibration plot (} \bar{D} = \frac{\sum_{i=1}^{N_{\text{cal}}} D_i}{N_{\text{cal}}} \text{) with } D_i \text{ the dose in the } i^{\text{th}} \text{ calibration point and } N_{\text{cal}} \text{ the number of calibration points.}
\]

The dose resolution depends on both the dose sensitivity of the gel and the scanning parameters. For R2 imaging of a gel dosimeter the number of echoes in a multiple spin echo experiment should be optimized for maximum dose resolution [42]. A table is provided in reference [42] that enables to extract the optimal number of echoes for any gel dosimeter (characterized by a specific R2 range).
4.2. Temperature dependence of the dose response upon irradiation

It is well known that reaction kinetics are influenced by the temperature at which the reaction takes place. Most reaction rate constants obey the Arrhenius relation:

$$ k = A e^{-\frac{E_a}{kT}} $$

The dose-R2 response is determined by the overall reaction rate of the radiation induced polymerization which depends on several reaction constants. Also the viscosity of the gel is determined by the temperature and may have a significant influence on the dose response. Large temperature dependencies have been observed in chemically polymerized solutions of AAm and Bis with low crosslink densities (5%T; 5%C) [43,44].

The dose-R2 response of PAG gels with high crosslink density appears to be relatively insensitive for temperature in the temperature range of 4°C to 22°C (figure 3a). At a temperature of 28°C a sudden drop in the dose-R2 sensitivity was observed. It should be noted that at that temperature (28°C) the gel became liquid (sol). A higher sensitivity for the irradiation temperature was found in a normoxic methacrylic acid based dosimeter gels (MAG polymer gel dosimeter) (figure 3b). In the case of the MAG polymer gel dosimeter, no gel-sol transition was observed at 30°C.

**Figure 3.** Dose-R2 plots for a PAG polymer gel dosimeter (a) and a MAG polymer gel dosimeter (b) irradiated at various temperatures.
4.3. Temperature dependence of the dose response upon scanning

As the movement of water molecules, monomers and polymer structures in solution increases with temperature the dipole-dipole interactions will be less efficient. As a result the $R_2$ of polymer gel dosimeters will decrease with increasing temperature. Temperature may also have an effect upon magnetization transfer and chemical exchange of protons. Both the slope as the intercept of the dose-$R_2$ response will decrease with temperature. Temperature coefficients of the dose-$R_2$ response have been published of PAG gel dosimeters [23,45] and of acrylic acid based gel dosimeters [46].

Dose-$R_2$ response curves at different scanning temperatures are shown in figure 4 for both an AAm/Bis polymer gel (6%T; 50%C) dosimeter and a normoxic MAc polymer gel (6%T) dosimeter. Similar response was found in a non-normoxic MAc polymer gel.

Figure 4. Dose-$R_2$ plots for a PAG polymer gel dosimeter (a) and a MAG polymer gel dosimeter (b) scanned at various temperatures. For the PAG gel, no measurement was performed above 25 °C as the PAG gel became fluid at a temperature around 28 °C.

From figure 3 it can be seen that, in this case, the temperature dependency is rather proportional to the dose sensitivity. This is not an expected outcome as the dose sensitivity of the two gel dosimeters is the result of different mechanisms. Further studies on the temperature dependency of relaxation rates may be useful in investigating the structural properties of polymer gel dosimeters.

The maximum dose inaccuracy of the gel dosimeter caused by a misinterpretation of the temperature during scanning amounts to 7–8% per degree Celsius for the PAG gel dosimeter in the linear dose region while for the MAG gel dosimeter the maximum dose inaccuracy is in the order of 4–5% per degree Celsius.

Although no studies on the temperature dependency have been communicated so far, it can be expected that with respect to the dose values, the optical properties are less sensitive to temperature. No studies have been reported on other scan techniques such as x-ray CT or ultrasound.
4.4. Stability of the dose response

Two kinds of long-term instabilities of the dose-R2 response have been found [4]. One affects the slope of the dose-R2 plot (dose sensitivity) and for the PAG gel dosimeter this is related to post-irradiation polymerization of the comonomer-polymer aggregates. In most polymer gel dosimeters the half-life time of this instability is in the order of several hours. The mechanism behind the decrease in dose sensitivity in MAG gel dosimeters is still unknown. The other instability affects the intercept of the dose-R2 plot, lasts for up to several days and is related to the gelation process of gelatin. Studies of the change in optical activity of gelatin gel indicate that the mechanism responsible for the gelatin-
related instability is through the formation of macromolecular collagen structures which provokes a change in the local mobility of water molecules [4]. This phenomenon, in the scientific literature often referred to as aging of gelatin gels, can be described by a three pool spin population model consisting of free water, unstructured bound water and structured bound water. In this model, the instability is caused by an increase in the population fraction of structured water at the cost of bound water. It has also been shown that the addition of a highly polar molecule, such as sodium-azide, may prevent the formation of collagen junctions and thus results in a more stable gel but at the cost of its rigidity. An alternative model has been proposed by Lepage et al [12] in which the increase in R2 is attributed to an ongoing gelation after the gel is set.

It is clear from figure 5 that while the change in R20 and dose sensitivity is larger in absolute terms for the MAG gel dosimeter compared to the PAG gel dosimeter, in relative terms of dose differences the MAG type dosimeter is more stable than the PAG gel dosimeter.

In order to obtain accurate dose maps it is advisable to scan the gel dosimeter and the calibration gel samples at the same moment. At this moment, no optical stability study has been reported.

4.5. Dose integrity

Another important property of a 3D gel dosimeter is the spatial stability. It is well known that in Fricke gel dosimeters the dose distribution is not preserved for a long time due to the diffusion of ferric and ferrous ions. In polymer gel dosimeters, another process can occur that is responsible for possible dose overshoots near steep dose gradients in combination with high doses.

From figure 6 it can be seen that the occurrence of dose overshoots is both dependent on the kind of gel dosimeter and the radiation dose absorbed in the irradiated area. The overshoots may also change with time after irradiation (figures 6a and 6c in comparison with 6b and 6d respectively).

The polymerization reaction that occurs at a specific location in the gel is dependent on the amount of monomer available at that specific location. From the temporal stability study, it is known that the polymerization still proceeds for several hours after irradiation. During this period, there is a net flux of “fresh” monomers from low dose regions to high dose regions (depleted in monomers). These “fresh” monomers will react with long-living polymer radicals that are present in the high-dose regions resulting in a dose overestimation. The spatial range in which a dose-overestimation is observed is dependent on the diffusion coefficient of the monomers in the gel and on the reaction rate (lifetime) of the long-living polymer radicals. This model has been quantitatively illustrated in a recent paper [47].

For the use of a certain polymer gel dosimeter it is very important to determine the upper threshold below which no overshoots occur. Attention should be paid to the fact that the occurrence of overshoots is time dependent. One should always use gel dosimeters in a dose range at which no overshoots occur during the time interval at which the dosimeters are read out.

For the development of new polymer gel dosimeters, in order to obtain gel dosimeters with good spatial integrity, two physico-chemical properties should be considered: (1) the diffusion coefficient of the monomers in the gel system should be as low as possible and (2) the lifetime of the polymer radicals should be as low as possible.
Figure 6. Lateral dose profiles at the edge of a rectangular field measured with a PAG gel dosimeter (a-b) and measured with a nMAG gel dosimeter (c-d) for different given doses. The saturation in the peak of figure (b) is related to the fact that R2 values in that region reach values above the calibration dose range. The values that can not be calibrated are artificially set at 50 Gy.

4.6. Dose rate dependence

The equilibrium concentration of water radicals present in pure water during radiation is dependent on the dose rate. The concentration of water radicals in water is determined by a competition between the creation of radiation induced radicals and the loss of radicals through termination reactions and is described by the differential equation [2]

\[
\frac{d[R^*]}{dt} = -k_T [R^*]^2 + k_G \dot{D}
\]  

(9)

with \(k_T\) the reaction rate constant for the termination reaction of radicals and \(k_G\) a yield constant of radical formation in a photon beam. \(\dot{D}\) is the dose rate. Equation (9) is a differential equation of the Ricatti type and can be easily solved by substitution yielding the solution.
\[
[R^*] = \frac{k_G \cdot D}{k_T} \left( 1 - \cosh^{-1}\left(2\sqrt{k_G \cdot k_T \cdot D \cdot t}\right) \right)
\]  

Figure 7 illustrates the dependence of radical concentration as a function of irradiation time. It can be seen that for clinical photon beams, the equilibrium radical concentration is not proportional to the dose rate. This simple example shows that the total amount of reactive radicals created in pure water for a given dose is dependent on the dose rate. However, it should be noted that in a gel containing much more monomers (0.5–1 M) than the number of water radicals that are created in pure water, the probability that water radicals react with a monomer is much greater than the probability of termination through recombination with other water radicals.

| Dose Rate  | \([R^*]_{eq}\)       |
|------------|-----------------------|
| 25 cGy/min | 2.08 \times 10^{-9} M |
| 50 cGy/min | 2.94 \times 10^{-9} M |
| 100 cGy/min| 4.16 \times 10^{-9} M |
| 200 cGy/min| 5.88 \times 10^{-9} M |
| 400 cGy/min| 8.32 \times 10^{-9} M |
| 1000 cGy/min| 1.32 \times 10^{-10} M|

Figure 7. The evolution of water radical concentration in pure water during radiation with a photon beam at various dose rates. The radical concentration reaches a steady state in the first second of the irradiation. The equilibrium concentrations are mentioned in the right column.

From figure 8 it can be seen that the dose rate at which gel dosimeters are irradiated may have a significant influence on the dose response. The sensitivity of the dose response to the dose rate is higher for the MAG gel dosimeters (figure 8b) compared to the PAG gel dosimeters (figure 8a). The dose-R2 sensitivity of both gel dosimeters is shown in figures 8d and 8c respectively. For both gel dosimeters the dose-sensitivity decreases with increasing dose-rate.

The dependence of dose response on the dose rate can be attributed to the rate at which radiation induced chemical processes occur. A change in the creation of reactive water radicals may then have an influence on the concentration of the different resulting products. The concentration of water radicals will dependent on the dose rate. As a result the average distance between the initiating radicals will be different. This may have an influence on the diffusion controlled propagation reactions and thus on the dose response of the gel dosimeter.

It is important to note that during a radiation treatment on a gel dosimeter phantom, the dose rate is spatially dependent. For a treatment in which more than one beam is involved the dose rate in any point in the phantom is even not simply proportional to the resulting dose in that point. This makes the dose rate sensitivity of a particular gel dosimeter an essential factor that determines the reliability. Polymer gels of which the dose rate dependence is too high should not be used as reliable 3D dosimeters.
Figure 8. Dose-R2 response for PAG gel dosimeters (a,c) and MAG gel dosimeters (b,d) irradiated at various dose rates. The dose sensitivity extracted from the linear dose region (shown in figures (a) and (b) by the dot-dashed lines) is shown in figures (c) and (d) for PAG and MAG gel dosimeters respectively.

4.7. Energy dependence

It is well known that the relative fraction of interaction processes is dependent on the type of radiation. A different photon energy will result in a different relative fraction of interaction processes. This may result in different fractions of water radiolytic products. As reaction rates of monomers with different water radiolytic products may differ, another dose response could be expected. The dose-R2 response curves of PAG and MAG gel dosimeters are shown in figure 9 for two different photon beam qualities (6 MV and 18 MV).
From figure 9 it can be seen that the change in dose-R2 response is not significant within the used dose range (0 to 10 Gy). For the MAG gel a significant difference between the 6 MV photon beam and 18 MV photon beam is seen at a dose of 15 Gy. However, it should be noted that the origin of this difference has not been reproduced so far and will be investigated in further studies.

Figure 9. Dose-R2 response of PAG gel dosimeter (a) and MAG gel dosimeter (b) for two different photon beam qualities (6 and 18 MV)

4.8. Tissue equivalence

Another important parameter of dosimeters for clinical applications is the equivalence between the measured dose and the dose absorbed in the patients’ tissue. This parameter, often referred to as “tissue equivalence” can be calculated by Monte Carlo calculations of depth dose curves using the photon end electron cross sections for the different chemical elements contained in the gel dosimeter [48]. It has been shown that the electron density is the dominant factor determining the water equivalence of the gel dosimeters [49].

Table 2 summarizes the main chemical elements and the electron density for different human tissues and for the PAG and MAG gel dosimeters. It can be seen that the mass density and electron density of PAG and MAG gel dosimeters is slightly higher than these of water and very close to muscle.

In order to obtain a lung equivalent gel dosimeter the density has to be decreased. This can be achieved by the addition of gas filled beads or by foaming the gel during manufacture. The major difficulties of a lung equivalent gel dosimeter however is the low MR signal and the diffusion attenuation of the MR signal caused by microscopic magnetic field gradients originating from the susceptibility differences between the gel and the beads.
Table 2. Composition of a typical PAG gel (6%T/50%C) and different tissue types. Mass and electron density are also given.

| atomic element | muscle | Bone | lung | water | PAG gel | MAG gel |
|----------------|--------|------|------|-------|---------|---------|
| H              | 10.1   | 3.4  | 10.13| 11.2  | 10.65   | 10.69   |
| C              | 17.1   | 15.5 | 10.24| -     | 6.203   | 7.41    |
| O              | 68.1   | 43.5 | 75.75| 88.8  | 80.96   | 80.51   |
| N              | 3.6    | 4.2  | 2.87 | -     | 2.182   | 1.39    |
| S              | 0.3    | 0.3  | 0.23 | -     | -       | -       |
| P              | 0.2    | 10.3 | 0.08 | -     | -       | -       |
| Ca             | -      | 22.5 | -    | -     | -       | -       |

| mass density | 1.04 g/cm³ | 1.40 g/cm³ | 0.296 g/cm³ | 1.0 g/cm³ | 1.035-1.042 g/cm³ | 1.046-1.05 g/cm³ |

| electron density relative to water | 1.0328 | 1.3492 | 0.293 | 1.0 | 1.031 | 1.044 |

Mass densities were experimentally determined in reference [27]. For both gel systems, the mass density increases slightly with absorbed radiation dose. The range of mass densities given in the table is for a dose range of 0 to 10 Gy for both gel dosimeters. The corresponding electron density is an average for the whole dose range.

4.9. Environmental variables during gel manufacture

4.9.1. Oxygen content. The oxygen concentration in a gel dosimeter can have a significant influence on the dose-R2 response. As mentioned before, oxygen has an inhibiting effect on “nitrogen purged” gel dosimeters. The effect of the inhibition by oxygen on the dose-R2 response is measured (figure 10).

Figure 10. Dose-R2 curves for various concentrations of oxygen (a) and corresponding correlation plot (b) of the dose threshold (Dₚ) as a function of the oxygen concentration.
The change in dose threshold with oxygen concentration in a PAG gel dosimeter (figure 10b) is given by

\[
\frac{\partial D_f}{\partial [O_2]} = 28.2 \text{ Gy mg}^{-1} l
\]  

(11)

It has been shown that the correlation between the dose threshold and the oxygen concentration can also provide interesting chemical data on the radiation chemical yield of the monomers [50].

In normoxic polymer gel dosimeters with ascorbic acid as anti-oxidant, oxygen also plays a role in the pre-irradiation polymerization. In this case, oxygen is bound in an ascorbic acid – copper complex that induces a polymerization reaction. As a result, the presence of small amounts of oxygen will lead to an offset in the R2-dose response [15]. At larger amounts of oxygen than the amount of ascorbic acid, inhibition will occur. In normoxic polymer gel dosimeters with other anti-oxidants the induced polymerization is not observed. The ability for the anti-oxidant tetrakis-hydroxy-phosphonium chloride to scavenge oxygen as a function of temperature obeys the Arhenius law representative for first-order kinetics.

4.9.2. Temperature treatment during manufacture. The temperature to which the gelatin solution is heated in order to obtain a sol determines the R2 value of the gelatin gel but does not have a significant influence on the time variation of R2 [4] (figures 11a and 11b).

\[\text{Figure 11. A different temperature treatment of a gelatin gel during manufacture (a) leads to different R2 values (b) while the temporal stability is not affected. The post-manufacture store temperature does not have a significant influence on the R2 (c) nor the slope of the PAG gel dosimeter (d). Solid symbols are for a PAG gel sample stored at 5 °C while filled symbols are for a PAG gel sample stored at 35 °C.}\]
Three different water pools can be discriminated: (a) the free water, (b) the water bound to gelatin macromolecules and (c) the structural water bound to the polypeptide chains in order to stabilize the triple helices or the aggregates of tropocollagen [51]. The resulting R2 value in the fast exchange limit can be written as

\[ R2 = P_f . R2_f + P_p . R2_p + P_{st} . R2_{st} \]  \hspace{1cm} (12) 

It is shown that the fraction of structural water being formed during gelation is not dependent on the temperature treatment of the sol [4]. However, the fraction of free water and the fraction of bound water are affected by the temperature treatment of the sol.

In a different study, the effect of the store temperature on the dose-R2 response was investigated [52]. From this study it was concluded that the store temperature did not have a significant impact on the dose-R2 response of the gel.

4.10. Reproducibility

4.10.1. Intra-batch reproducibility. The intra-batch reproducibility of a PAG gel dosimeter was investigated by irradiating 20 gel samples from the same gel batch with a dose of 10 Gy. The measured R2 values are shown in figure 12a. The error bars in figure 12a correspond to the standard deviation of the different R2 pixel values in a region-of-interest corresponding to a homogeneously irradiated cross-section of the gel sample. The corresponding distribution is shown in figure 12b. A measure of the intra-batch reproducibility is given by the standard deviation of the Gaussian fit on the R2 distribution and amounts to 0.012 s\(^{-1}\) or 0.9 % of the total dose range.

Figure 12. Intra-batch reproducibility. Figure (a) shows the different R2 values of various PAG gel dosimeters from the same batch all irradiated with 10 Gy. The corresponding histogram is shown in (b). A Gaussian fit was applied as a guide to the eye. The dashed line in figure (a) corresponds to one standard deviation of the Gaussian fit.

4.10.2. Inter-batch reproducibility. Figure 13 shows the intercept (a) and slope (dose-sensitivity) (b) of the dose-R2 response of different PAG gel dosimeters. The PAG samples were fabricated on different moments and by different researchers. In order to make a fair comparison, also the instability of the different gel dosimeters has to be taken into account. The maximum standard deviation on the intercept amounts to 0.08 s\(^{-1}\) while the variation on the slope (or dose-sensitivity) amounts to 0.02 s\(^{-1}\) Gy\(^{-1}\) or 20 % of the dose. It should be noted that the data presented here was collected from different studies that were set-up individually without the aim to reproduce the gels.
Figure 13. Inter-batch reproducibility in R2₀ (a) and in slope (b) of five different batches of PAG gel dosimeter. The dot dashed curve in (a) derived by a mono-exponential fit corresponds to the change in R2 values from chemical instability.

From these results it can be concluded that all gel dosimetry experiments should be conducted with calibration samples that originate from the same batch of gel. It should be noted that the manufacturing of PAG gel dosimeters is rather time consuming. Until now, reproducibility studies have only been conducted for PAG gel dosimeters. As normoxic gel dosimeters can be fabricated in a shorter time span, it is advisable and straightforward to retake the reproducibility studies for these gel dosimeters.

5. Conclusions

Different properties should be investigated first for each new gel dosimeter before usage in order to guarantee the accuracy of the dose measurement. Different characteristics were found for various gel dosimeters. Although in the literature, many authors have focused on the dose-resolution, even more important for the accuracy and reliability of the gel dosimeter are properties such as dependence on temperature during irradiation and scanning and dose-rate dependency. New polymer gel dosimeters with a high dose-rate dependency should not be promoted as “potential” gel dosimeters.

Important to the usage of polymer gels for 3D radiation dosimetry is also to commit to a “code of good practice”. As such, when using NMR as a read-out technique, gel dosimeters should be scanned together with the calibration samples in order to avoid differences in dose-R2 response between the dosimeter phantom and the calibration samples that are related to temperature differences or temporal instability. The gel dosimeters should be stored at least one day before scanning in the MR scan room in order to obtain a uniform temperature throughout the whole phantom. Gel dosimeters should be used only in a dose range in which no dose overshoots occur.
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