An experimental study of the dose response of polymer gel dosimeters imaged with x-ray computed tomography

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Abstract
Changes in the linear attenuation coefficient of polymer gel dosimeters post-irradiation enable the imaging of dose distributions by x-ray computed tomography (CT). Various compositions of polymer gel dosimeters manufactured from acrylamide (AA), and \(N,N'\)-methylene-bis-acrylamide (BIS) comonomers and gelatin or agarose gelling agents were investigated. This work shows that increasing the comonomer concentration increases the CT-dose sensitivity of the polymer gel dosimeter. This can be further increased by replacing gelatin with agarose. Varying the gelatin concentration however does not significantly change the CT-dose sensitivity. Among the compositions studied, dose resolution \(\frac{D}{\Delta_{95\%}}\) was found to be optimal for polymer gel dosimeters comprising 5% gelatin, 3% AA, 3% BIS and 89% water.

1. Introduction

There is a need in radiotherapy to accurately measure three-dimensional (3D) absorbed dose distributions from irradiation techniques such as intensity-modulated radiotherapy, stereotactic radiosurgery and high dose rate brachytherapy. Dosimeters currently in use, such as ionization chambers and thermoluminescent dosimeters, have limitations as they only measure the dose at a single point, and radiographic films only measure a 2D distribution.

In 1984, it was proposed that magnetic resonance imaging (MRI) could be used to measure dose distributions produced by ionizing radiation absorbed in aqueous gels infused with a ferrous sulfate dosimeter solution (Gore et al 1984). Subsequently, dose distributions were measured based on radiation-induced polymerization of acrylic monomers (Maryanski et al...
Table 1. Composition and measurement results of the various polymer gel dosimeters used by percentage of the final weight. $r^2$, standard error and $P$-value are taken from the regression program in Microsoft® Excel. Minimum detectable dose is defined in the text.

<table>
<thead>
<tr>
<th>Gelling agent by % weight</th>
<th>Monomers by % weight</th>
<th>Water by % weight</th>
<th>CT-dose sensitivity (H$_{\text{T}}$/Gy)</th>
<th>$r^2$</th>
<th>Standard error (Gy)</th>
<th>$P$-value</th>
<th>Minimum detectable dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelatin</td>
<td>Agarose</td>
<td>AA</td>
<td>Bis</td>
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<td>3</td>
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1993, 1994). Since then there has been a growing body of research into the use of radiosensitive gels with the intention of introducing them clinically as 3D dosimeters (Schreiner 1999). However, to date gel dosimeters have not achieved routine clinical use. For reviews of gel dosimetry see Schreiner (1999) and McJury et al (2000).

One of the factors impeding the routine use of polymer gel dosimeters clinically has been the difficulty involved in extracting accurate dose information through medical imaging techniques. The main imaging modality of choice to date has been MRI. Although the potential of MRI in imaging polymer gel dosimeters has been demonstrated, image plane inhomogeneities and lengthy imaging times are included in the current limitations. Additionally, the transverse relaxation time, $T_2$, is temperature sensitive, which means that polymer gel dosimeters evaluated by this method must be brought to a stable temperature prior to imaging (Maryanski et al 1997). Temperature drift in the polymer gel dosimeter during imaging can cause a change in $T_2$ (De Deene and De Wagter 1999).

There are alternative methods currently under investigation for extracting dose information such as optical tomography (Gore et al 1996) and vibrational spectroscopy (Baldock et al 1998b).

A recent feasibility study indicated that x-ray computed tomography (CT) is a promising alternative method for evaluation of polymer gel dosimeters due to a change in the linear attenuation coefficient with increasing dose (Hilts et al 2000). In this paper we aim to further examine the potential of CT imaging of polymer gel dosimeters.

2. Materials and methods

2.1. Polymer gel dosimeter manufacture

Polymer gel dosimeters were manufactured with varying concentrations of acrylamide (AA) (Sigma Aldrich, Sydney) and $N,N’$-methylen-bis-acrylamide (BIS) (Sigma Aldrich, Sydney) comonomers dissolved in a matrix of aqueous gelatin (300 bloom) (Sigma Aldrich, Sydney) or agarose (FMC Bioproducts, Rutherford) (table 1). The polymer gel dosimeters were produced in a nitrogen-filled glovebox using methods previously described (Baldock et al 1998a). After production, the gel was poured into 20 ml polyethylene liquid scintillator vials (diameter
27 mm, wall thickness 1 mm, length 60 mm) (Packard, Meriden). Plastic vials were used instead of glass vials to minimize x-ray beam hardening during imaging.

Due to the scavenging of free radicals by oxygen (Vollmert 1973), radiation-induced polymerization is potentially inhibited in polymer gel dosimeters contained within plastic-walled phantoms (Maryanski et al. 1994, Bonnett et al. 1999). To minimize this effect the vials were heat sealed in pouches made from 0.1 mm thick Barex sheets (Arbo Plastic Ltd, Switzerland) prior to removal from the nitrogen atmosphere of the glovebox used for manufacture. Barex has low permeability to oxygen (BP 2000) and was previously used for manufacture of polymer gel dosimetry phantoms (Baldock et al. 1996). The use of this material ensured that the vials were kept in an oxygen free atmosphere.

The pouches containing the vials of polymer gel were then cooled in water at approximately 10°C for approximately 1–2 h until a visual inspection revealed that they had set. They were subsequently kept at room temperature and irradiated in their Barex pouches after a further 1 h.

2.2. Irradiation

The polymer gel dosimeters were irradiated in their Barex pouches at a dose rate of 12 Gy per minute up to 50 Gy in a $^{60}$Co Gammacell 200 (Atomic Energy of Canada Ltd) which had previously been calibrated (Baldock et al. 1999a). The gels were removed from the pouches and exposed to oxygen after three days as the majority of the polymerization reactions have occurred by that time (Baldock et al. 1999b, McJury et al. 1999, De Deene et al. 2000). Exposure to oxygen stabilized the polymer gel dosimeter ensuring all samples experienced the same conditions post-polymerization. Exposure was achieved by removal of the lid of the vials for approximately 5 min at both 3 and 4 days after irradiation. Longer exposure times were avoided to prevent dehydration of the polymer gel dosimeters. The vials were then left for at least two days prior to imaging to allow diffusion of oxygen throughout the entire gel.

2.3. Phantom

The phantom used to image the polymer gel dosimeter vials consisted of a 25 cm external diameter cylindrical perspex ‘holding’ tank of 5 mm thick walls attached to a square ‘access’ tank (figure 1). The vials were held in place by high-density styrene machined to fit inside the holding tank. Boundary and beam hardening effects were prominent within 2 cm of the air–perspex–water interface. The phantom was filled with water to reduce these artifacts with the vials placed 2.5 cm from the inside perspex wall of the phantom in a circular arrangement (figure 2(a)). The artifacts, if present, affected all vials equally as they were placed equidistantly from the phantom wall. Images were acquired of the central cross-sectional plane of the vials. The design of the phantom allowed images to be acquired through the portion of the vials protruding out of the styrene into the water. All vials could then be moved away from the slice location along the length of the holding tank while remaining inside the phantom. This allowed subsequent images to be acquired of water only in exactly the same position (relative to the CT scanner) as the vials.

2.4. Imaging

Imaging was performed using a Picker PQ5000 CT scanner. The highest kV (140 kV) and tube current (400 mA) available were used with an exposure time of 1.5 s. This allows maximum number of photons to reach the detectors thereby reducing noise (Zacher 1977). To further
reduce noise, twenty 5 mm slices were acquired and averaged for each polymer gel dosimeter composition. Imaging time using this method was approximately 10 min. Sixty-four images were acquired on one occasion for examination of noise characteristics.

The images were transferred to a personal computer and processed using the image processing toolbox in MATLAB™ software (The Mathworks, Inc). Circular regions of interest (ROI) of 230 pixels were drawn in the area of the image corresponding to the polymer gel dosimeter inside the vials.

2.5. Mass density

Two different glass volumetric flasks (50 ml) with capillary stoppers were used to determine the density, $\rho$, of the polymer gel dosimeter (composition 5% gelatin, 3% AA, 3% bis, 89% water) before and after irradiation. One sample was irradiated inside the Gammacell 200 to a dose above 50 Gy to ensure the majority of the monomers were polymerized, while the other sample was left unirradiated.

The density of the gel was calculated as

$$
\rho_{gel} = m_{gel} \left( \frac{\rho_{water}}{m_{tot} - m_{wall}} \right)
$$

Figure 1. The phantom consists of a 25 cm diameter cylindrical tank and removable styrene insert which holds the polymer gel dosimeter vials. An image is taken through the portion of the vials protruding into the water and another image is taken through exactly the same location after the vials have been removed. The second image is subtracted from the first to give the final image.
where $\rho_{\text{gel}}$ is the density of the polymer gel dosimeter, $\rho_{\text{water}}$ is the density of water, $m_{\text{tot}}$ is the mass of water that the flask can hold, $m_{\text{wat}}$ is the mass of water required to fill the flask when containing gel and $m_{\text{gel}}$ is the mass of gel in the flask.

The CT number ($H$) of both flasks were measured using the CT scanner with the same parameters as described above (section 2.3). The data were averaged using ten slices and the mean value and standard deviation were measured in an ROI (400 pixels) corresponding to the centre of the flask.

2.6. Dose uncertainty and dose resolution

The standard uncertainty ($U(D)$) (ISO 1995) in the measured absorbed dose ($D$) can be assessed by examination of the gel response ($r$), defined as the reading of the dosimeter at a given dose ($H$) and the CT-dose sensitivity, $dr/dD$ (Attix 1986).

$U(D)$ was calculated using a first-order Taylor expansion of the parameters of a calibration function fit to the data (see section 3). The dose resolution ($D_{\text{p}}/\Delta D$) is defined as the minimal separation between two absorbed doses so that they can be distinguished with a specified level of confidence, $p$ (Baldock et al 2001):

$$D_{\text{p}}^h = k_p \sqrt{2} U(D).$$

(2)

For a confidence level of 95% and large number of degrees of freedom, the coverage factor, $k_p$, is 1.96 (ISO 1995, Baldock et al 2001).

3. Results and discussion

3.1. CT measurements

The image of the phantom containing only water was subtracted from the image containing the polymer gel dosimeter vials and water, thereby significantly reducing artifacts such as beam hardening (figure 2(a)). Rounding of the phantom edges to the nearest pixel location during reconstruction causes different partial volume effects in each image which are highlighted by the subtraction process (figure 2(b)). This did not however affect the polymer gel dosimeters as these have similar CT signals to water and therefore no high contrast edges existed in close proximity to the vials.

The results from the measurements are shown in table 1. Figures 3(a)–(c) show the CT-dose response of the gels. Also shown are mono-exponential fits to the experimental data. It is visually apparent that a mono-exponential function fits all curves well. The function is of the form

$$H = y + A \exp\left(-\frac{D}{t}\right)$$

(3)

where $y$, $A$ and $t$ are the fit parameters of the function.

In scanning polymer gel dosimeters using MRI, it is common practice to obtain a calibration graph from a linear fit to the quasi-linear increase of $R_2$ at low doses. A divergence from linearity has been repeatedly observed (Ibbott et al 1997, Oldham et al 1998, De Deene et al 2000, Lepage et al 2000, Murphy et al 2000). However, an assumption of linearity is often still used for a limited dose range. To investigate whether a linear fit could be assumed for CT of polymer gel dosimeters, a chi-square test was performed on the exponential and linear fits in the 0–10 Gy region for gelatin gels and 0–8 Gy region for agarose gels. The linear fit was shown to have the lowest chi-square value. These regions were therefore approximated.
as linear and are referred to as the ‘linear region’ for the remainder of this paper. The linear region is shown in the inserts in figures 3(a)–(c) with linear fits.

A comparison of figures 3(a)–(c) shows that varying monomer concentrations (AA + BIS) affects both the overall CT-dose response and the CT-dose sensitivity. If gelatin is replaced by agarose as the gelling agent there is a further increase in CT-dose sensitivity and the overall CT-dose response tends to be shifted to lower CT numbers. A variation in the gelatin concentration predominantly affects only the overall CT-dose response. The CT-dose sensitivity is increased by increasing the monomer concentration, with the limit being the ability to physically manufacture gels with high concentrations of monomers. If the gelatin concentration is increased there is a decrease in CT-dose sensitivity; however, the change is much less apparent than the case where monomer concentration is varied. This is consistent with results obtained with MRI studies (Audet et al 1995, Maryanski et al 1997).

In their feasibility study, Hiits et al achieved a CT-dose sensitivity of $(0.86 \pm 0.04) \times 10^{-3}$ H Gy$^{-1}$ for a polymer gel dosimeter composed of 5% gelatin, 3% BIS, 3% AA and 89%
Figure 3. CT-dose response for gels with varying concentrations of acrylamide (AA) plus \(N,N'\)-methylen-bis-acrylamide with gelatin (a) and agarose (b), and varying gelatin concentration (c). The linear region is shown in the inserts.
water (Hilts et al. 2000). We obtained a comparable CT-dose sensitivity of $(0.71 \pm 0.02) \times 10^{-3} \text{ H Gy}^{-1}$ for the same composition (table 1).

Figure 4 shows the standard deviation in CT numbers for all the polymer gel dosimeters with different monomer concentrations. The noise appears to be approximately constant in the linear region. This is in contrast to MRI where the noise has a dependency on $1/T_2$ and thus on dose (De Deene et al. 1998, Baldock et al. 1999c).

Figure 5 is a plot of the standard deviation of CT numbers in an ROI taken in the central portion of the phantom, inside the circumference formed by the polymer gel dosimeter vials. This figure shows the standard deviation obtained from the original image of the vials, the water image to be subtracted from the original image and the final image post-processed. A curve of the form $n^{-1/2}$ was fitted to the data for the final image, where $n$ is the number of images averaged. The noise from the final subtracted image is greater than that of the original images. This increase in noise by a factor $\sqrt{2}$ is due to the combined variances of the original image of the polymer gel vials and the water image. Although the process of subtraction increases the noise, it is essential to reduce systematic errors. For example, the mean CT number of the ring artifact as seen in figure 2(a), was measured to be up to 1 H different from the surrounding area and is located in the polymer gel dosimeter vials. After averaging several images together the noise due to photon counting statistics can be reduced, however, the total noise in the CT image tends asymptotically to a value of approximately 0.6 H. This is a known effect in CT imaging and is due to factors such as reconstruction noise, electronic noise and CT number quantization (Cohen and Di Bianca 1979).

$U(D)$ can be found with the first-order Taylor expansion of equation (3):

$$U(D) = \sqrt{\sigma_y^2 \left( \frac{\partial D}{\partial y} \right)^2 + \sigma_H^2 \left( \frac{\partial D}{\partial H} \right)^2 + \sigma_A^2 \left( \frac{\partial D}{\partial A} \right)^2 + \sigma_t^2 \left( \frac{\partial D}{\partial t} \right)^2}$$

(4)

where $\sigma_y$, $\sigma_A$ and $\sigma_t$ are the uncertainty in the fit parameters $y$, $A$ and $t$ in equation (3).
As the data points for the calibration curve are taken from ROIs containing 230 pixels and not single points, the best estimate of the uncertainty in pixel values within the region of interest is given by the experimental standard deviation of the mean, $\sigma_H$ (ISO 1995):

$$\sigma_H = \frac{s_H}{\sqrt{n}}$$

(5)

where $s_H$ is the experimental standard deviation of pixel value within an ROI in Hounsfield units and $n$ is the number of pixels within the ROI.

An assessment of $D_{95\%}^\Delta$ is shown in figure 6 for all polymer gel dosimeters where the total monomer concentration is varied, corresponding to the dosimeters with the greatest to the least sensitivity. It is seen that the optimal $D_{95\%}^\Delta$ was achieved with a composition of 5% gelatin, 3% AA, 3% Bis and 89% water. The low CT-dose sensitivity of the polymer gel dosimeter with lower concentrations of monomers accounts for the higher $D_{95\%}^\Delta$ in the formulations containing 1% and 2% monomer concentrations. The intuitive assumption that $U(D)$ would be optimal for the polymer gel dosimeter with the greatest CT-dose sensitivity (5% and 6% monomer concentrations for the gelatin based dosimeters, and both agarose based batches) is negated by the fact that the calibration function better fits the polymer gel dosimeters in the mid to lower region of monomer concentrations due to a lesser spread of data points around the function. This results in lower values for $\sigma_y$, $\sigma_A$ and $\sigma_t$ of equation (4) and shows that good experimental practice is essential for improving $D_{95\%}^\Delta$.

In this set of measurements the resulting $D_{95\%}^\Delta$ (equation (5)) indicates that the minimum detectable dose (MDD), defined as $D_P^\Delta$ as the dose approaches zero (Baldock et al 2001), is 1.0 Gy for the composition of 5% gelatin, 3% AA, 3% Bis and 89% water. These values are
higher than measured with MRI (Baldock et al. 2001), however, further optimization could considerably improve this result.

Equation (4) shows some dependency of $D_{\Delta H}$ on $\sigma H$. Examination of figure 5 shows that increasing the number of image acquisitions (or effective mAs) will further reduce $\sigma H$ by up to 30–40%. Future development in detector and CT design will also reduce noise and thus $D_{\Delta H}$. Furthermore, in this work the phantom was large (25 cm of water). Smaller phantoms will allow many more photons to reach the detectors thereby greatly reducing noise (Zacher 1977). The noise in the measurements is also dependent upon factors such as x-ray energy, tube current, efficiency of individual detectors and/or machines and number of pixels sampled.

3.2. Density measurements

The relative mass densities compared to water were found to be 1.021 g cm$^{-3}$ and 1.035 g cm$^{-3}$ for the unirradiated and irradiated polymer gel dosimeter, respectively, with uncertainty of 0.002 g cm$^{-3}$ for each measurement found through standard propagation of uncertainties in equation (1). The result for the unirradiated gel was in excellent agreement with previous published data (Keall and Baldock, 1999). The corresponding CT numbers from the image of the flasks were determined as 21 H and 35 H, with experimental standard deviations of the measurement being 2 H each.

The parameter of interest is the CT-dose response pre- and post-irradiation to a certain given dose, i.e.

$$\Delta H = \frac{1000}{\mu_{\text{water}}}(\mu_{\text{post-irr}} - \mu_{\text{pre-irr}}) \approx 1000 \left(\frac{N_c}{\sigma_c}\right)_{\text{gel}} \left(\frac{N_c}{\sigma_c}\right)_{\text{water}} \left(\rho_{\text{post-irr}} - \rho_{\text{pre-irr}}\right) \left(\rho_{\text{water}}\right)$$ (6)
where $H$ is defined as

$$H \equiv 1000 \frac{\mu_{\text{gel}} - \mu_{\text{water}}}{\mu_{\text{water}}}$$

and the linear attenuation coefficient, $\mu$, for each constituent is

$$\mu = N_e \sigma_e \rho$$

where $N_e$ is the number of electrons per mass unit and $\sigma_e$ is the cross-sectional area per electron.

The approximation above is valid according to the ‘mixture rule’ (Hubbell 1982) as $\mu$ for a given material can be calculated using the individual cross section of each atomic species and their relative fraction in the material. The actual molecular structure has a minor effect on the cross section for photons with energies above 10 keV. In the case of irradiation of the polymer gel dosimeter, the atomic composition is identical before and after irradiation, indicating that the significant radiological parameter that changes from unpolymerized to polymerized gel is essentially the mass density. This assumption was verified by the measurement of the density and the CT number for unpolymerized and polymerized gel. The measured densities resulted in a calculated $\Delta H$ (equation (6)) of $14 \pm 1$ using a relative electron density and cross section (gel–water) from previous published results, mean photon energy 70 keV (Keall and Baldock 1999) compared with the CT number measured in the CT images of $14 \pm 2\,\text{H}$.

The density decrease corresponds to a calculated volume change of the order of 1.5%. Depending on the irradiation geometry and the spatial resolution of the evaluation there may be situations where this effect cannot be disregarded. The spatial extension of an irradiated volume will accordingly always be slightly underestimated.

The change of density will also change the radiation absorption properties leading to an increased uncertainty in and behind large irradiated volumes as the radiological properties change. There may be some situations where this effect cannot be disregarded, for example, using low dose rate irradiation techniques with gel mixtures which polymerize quickly. Further examination of this effect however is beyond the scope of this paper and left for future studies.

4. Conclusion

It is shown that CT can be used to measure radiation induced changes in the linear attenuation coefficient of polymer gel dosimeters. The change in linear attenuation coefficient is likely to be due to an observed increase in mass density.

The CT number increases as absorbed dose increases. The CT-dose sensitivity of the gel can be increased by increasing monomer concentration, or by using an agarose-based polymer gel dosimeter; however, the composition which produces the greatest CT-dose sensitivity does not necessarily produce the optimal dose resolution.

Although the minimum detectable dose is greater than that obtained using MRI, considerable improvements are yet to be made and will result from optimization of technique.

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