Micelle hydrogels for three-dimensional dose verification

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Abstract Gelatin hydrogels form a transparent and colourless matrix for polymerization or chromic reactions initiated by absorption of ionizing radiation. Generally, hydrogel chemistries have been limited to water soluble reactants. Work to adapt a water insoluble colourless leuco dye to coloured dye conversion reaction in hydrogels, led to the idea that micelles (i.e. tiny aggregates of surfactant molecules) may provide the necessary polar and nonpolar hybrid environment. Both leucomalachite green and leuco crystal violet radiochromic gels have been developed as three-dimensional (3-D) radiochromic dosimeters for optical computed tomography (CT) scanners. It has been found that the post-irradiation diffusion rates strongly correlate with the solubility of the leuco dyes. Since the crystal violet dye is more soluble in the micelle than in the surrounding water, the dose distribution degrades at the slower rate of micelle diffusion, thus yielding stable images of dose. A dosimetric characterization of leucomalachite green and leuco crystal violet gels, respectively, reveals that tissue equivalent micelle hydrogels are promising dosimeters for radiation therapy 3-D dose verification.

1. Introduction
The simple optical absorption spectrum of a gel containing only a single dye species is desirable for quantitative optical computed tomography (CT) scanning. Ferrous xylenol-orange gels exhibit a composite of at least four species that absorb light, with their yields being dose dependent [1]. Polymerization gels have a distribution of molecular weights that complicate quantitative analysis of attenuation profiles. Colourless, transparent hydrogels are spectrally ideal for three-dimensional (3-D) radiation dosimetry with optical CT readout. The lack of initial absorbance allows gels with optical pathlengths of greater than 20 cm to be efficiently scanned. Many radiochromic chemistries have been investigated for radiation dosimetry. One popular approach has involved conversion of a colourless material or solution to a coloured one. Most of the chemistries have involved non-aqueous systems. This work reports on the successful adaptation of a colourless leuco triphenylmethane dye to coloured dye conversion reaction using micelles (i.e. aggregates of surfactant molecules) which provide the required hybrid environment to dissolve these dyes into a hydrogel. Two different leuco dyes were investigated: leucomalachite green (LMG) and leuco crystal violet (LCV). It has been found that the post-irradiation diffusion rates correlate well with the solubility of leuco dyes [2]. Since the crystal violet dye is more soluble in the micelle than in the surrounding water, it was hypothesized that the dose distribution
will degrade at the slower rate of micelle diffusion, thus yielding stable images of dose. In some situations, radiochromic hydrogels may be preferable for use over transparent 3-D polyurethane plastics (PRESAGE™) which also contain a leuco dye and have a similar optical performance to gels [3], since the radiochromic plastics are likely to limit dosimeter size due to the cost of the raw materials and complexity of manufacturing large volume dosimeters.

2. Methods and Materials

2.1 Hydrogel preparation
A systematic examination of surfactants revealed that Triton X-100 provided adequate solubility to keep both LMG dye and LCV dye dissolved in 4% gelatin hydrogels. LCV micelle gel samples were prepared by dissolving LCV dye (Sigma-Aldrich), surfactant Triton X-100 (Sigma-Aldrich) and trichloroacetic acid (Mallinckrodt) into a solution of 4% by mass 300 bloom porcine gelatin (Sigma G-2500) and distilled water. LMG micelle gel samples were prepared in a similar way except that LMG dye (Sigma-Aldrich) was used in place of LCV dye. The reactant concentrations were varied to determine the optimal gel sensitivity defined as the change in optical attenuation coefficient per unit radiation dose for both hydrogel samples, respectively.

Upon preparation, the aqueous radiochromic gelatin solutions were poured into 1 cm polymethylmethacrylate (PMMA) cuvettes and allowed to gel overnight in a refrigerator at 5ºC. Additionally, from the same batch, bulk gel samples were prepared in 1 L polyethylene terephthalate (PETE) cylindrical jars.

2.2 Irradiation procedure
The next day post gel manufacture, cuvettes were returned to room temperature (20ºC). For the dosimetric characterization experiments, gel-filled cuvettes were irradiated in a water equivalent plastic cuvette holder using parallel-opposed-pair cobalt-60 beams (average of 1.25 MeV γ-rays) to doses between 0 – 30 Gy. The bulk 1L gel samples were irradiated with a 12 MeV electron beam (Varian Clinac 2100C, 100 cm source to surface distance, 6x6 cm² field size) to a dose of 30 Gy at depth of 30 mm. For the diffusion rate experiments, a parallel-opposed beam irradiation with a 6 MV X-ray beam (Varian Clinac 2100C) was applied only to one half of a cuvette filled with LCV gels made with and without surfactant Triton X-100 and LMG gels, respectively. A lead block was used to shield half of the cuvette in order to generate a step-shaped edge profile.

2.3 Hydrogel optical transmission measurements
An absorption spectrum over the visible wavelength region (400 – 650 nm) was initially measured for a gel cuvette sample irradiated to varying doses in order to determine the optimal readout wavelength. At 20 minutes post-irradiation, optical transmission was measured through individual gel-filled cuvettes and referenced to a water-filled cuvette at 590 nm for LCV gels and 633 nm for LMG gels, using an absorption spectrophotometer (Perkin-Elmer 139). The change in the attenuation coefficient, Δμ, per unit dose interval was then measured with respect to the non-irradiated gel sample.

The bulk 1L gel samples were scanned 20 minutes post-irradiation using a commercial cone-beam optical CT scanner (Vista™, Modus Medical Devices Inc.) at a central wavelength frequency of 590 nm and 633 nm for LCV and LMG gels, respectively. 512 projections were collected over 360° with each projection averaged to yield a reconstructed pixel size of 0.5 mm. From the optical CT reconstruction, the central-axis change in optical attenuation with depth in the respective hydrogel was fit against the TG-21 corrected ion chamber central-axis depth dose data measured for the electron beam in water.

2.4 Hydrogel diffusion rate measurements
The change in optical density measurements through 1 cm pathlength were collected using a focused laser beam (λ = 594, spot size ~ 0.2 mm) along the length of each cuvette to sample the
step-shaped edge profile across the unirradiated to irradiated regions. Optical transmission profiles were acquired from times of 0.33 to 23.5 hours after irradiation in order to determine the respective hydrogel diffusion coefficients (mm² hr⁻¹).

3. Results and Discussion
The change in the LCV gel absorption spectrum with increasing absorbed dose exhibited a peak near 600 nm. The spectral data for the LMG gel showed a distinct peak at 633 nm. These results suggest that readily available yellow and red light sources (i.e. laser, light emitting diode) are an optimal choice for optical attenuation measurements with LCV and LMG gels, respectively.

The most radiation sensitive LMG gel formulation contained: 4% gelatin, 6 mM Triton X-100, 15 mM trichloroacetic acid and 0.1 mM leucomalachite green dye. For the LCV gel, the optimal formulation was: 4% gelatin, 4 mM Triton X-100, 30 mM trichloroacetic acid and 1 mM leuco crystal violet dye. With these reactant concentrations, the maximum dose response for the LCV and LMG gels, respectively, was 0.012 cm⁻¹Gy⁻¹ at 590 nm and 0.005 cm⁻¹Gy⁻¹ at 633 nm. For both hydrogels, the dose response was linear over the studied dose range of 0 – 30 Gy.

The optical density profiles along the length of a half-irradiated cuvette filled with LMG gel is shown as a function of time in figure 1. Table 1 summarizes the measured diffusion rates for LCV gels made with and without surfactant, as well, LMG gels. LMG gels had a diffusion coefficient equal to 0.31 ± 0.01 mm² hr⁻¹.

| Radiochromic Gel | Diffusion Coefficient (mm² hr⁻¹) |
|------------------|---------------------------------|
| LMG              | 0.31 ± 0.01                     |
| LCV (no surfactant) | 0.33 ± 0.02                    |
| LCV (with surfactant) | 0.036 ± 0.001                  |

Table 1 Measured diffusion coefficients for LMG and LCV gels with and without surfactant, respectively.

![Figure 1 Optical density line profiles through the length of a half-irradiated LMG gel-filled cuvette at different time points.](image)
This value was comparable to the diffusion rate of LCV gels made without surfactant Triton X-100 which was found to be 0.33 ± 0.02 mm² hr⁻¹. Adding Triton X-100 lowered the diffusion coefficient of LCV gels by a factor of 10 to 0.036 ± 0.001 mm² hr⁻¹. The latter result validates the hypothesis that the diffusion rate of the crystal violet dye is coupled to that of the micelle thereby increasing the post-irradiation dose stability. The low diffusion rate coupled with near water and tissue equivalency (see tables 2 and 3), suggests that radiochromic micelle gels may be a promising alternative for quantitative 3-D gel dosimetry. Presently, the lower dose sensitivity (~10-20 times less than the ferrous xylenol-orange gel) is an inferior property of these gels but it is anticipated that we can overcome this limitation with additional chemical additives (i.e. halocarbons) or purifying the dyes by recrystallization [4].

| Material     | H  | C  | O  | N  | P  | S  | Cl | K  |
|--------------|----|----|----|----|----|----|----|----|
| LCV gel      | 0.100 | 0.124 | 0.024 | 0.729 |    |    | 0.022 |    |
| LMG gel      | 0.102 | 0.110 | 0.025 | 0.752 |    |    | 0.011 |    |
| Water        | 0.112 |    |    |    |    |    | 0.888 |    |
| Muscle (ICRU)| 0.102 | 0.123 | 0.035 | 0.729 | 0.001 | 0.0002 | 0.002 | 0.005 | 0.003 |

Table 2 The elemental composition (in weight fractions) of the two different radiochromic micelle gels compared to water and striated muscle.

| Material     | Physical density (kg m⁻³) | Electron density (x 10²⁹ elec m⁻³) | Electron density relative to water | *Zₜeff (photoelectric) | **Zₜeff (pair production) |
|--------------|---------------------------|-----------------------------------|----------------------------------|------------------------|-------------------------|
| LCV gel      | 1005 ± 5                  | 3.3682                            | 1.0076                           | 7.46                   | 6.61                    |
| LMG gel      | 1015 ± 5                  | 3.3692                            | 1.0079                           | 7.43                   | 6.60                    |
| Water        | 1000                      | 3.3428                            | 1.000                            | 7.42                   | 6.60                    |
| Muscle, striated | 1040                 | 3.4450                            | 1.031                            | 7.46                   | 6.54                    |

Table 3 The physical density, electron density and effective atomic number (Zₜeff) of LCV and LMG gels compared to water and muscle. The exponent in the Zₜeff calculation was *2.94 [5] and **1.00 [6].

Figure 2 shows a post-irradiation transmission image (camera view) of the LMG gel irradiated with a 12 MeV electron beam (a) and the corresponding cone-beam optical CT reconstructed image (b). A comparison of the central axis LMG gel attenuation coefficients normalized at depth of maximum dose (dₘₐₓ) with TG21-corrected ion chamber data, demonstrated agreement only in the buildup region (figure 3a). Beyond dₘₐₓ, the LMG gel over-responded but it was found that this spatial error could be eliminated by pre-exposing the LMG gels to a uniform ‘priming’ dose of 5 Gy. The reason for this is the subject of future work. LCV gels on the other hand, exposed to the same 12 MeV electron beam, showed agreement with ion chamber data at all depths (figure 3b) thereby confirming energy and dose-rate independence.
4. Conclusions
By using micelles, leuco dyes can be dissolved to provide transparent, colourless hydrogels. Radiochromic LCV micelle gels in particular show little diffusion effects and a dose response that is linear, energy and dose rate independent. Micelle hydrogels may be an alternative to radiochromic plastics for 3-D radiation therapy dosimetry.

5. References
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