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Tetrazolium salt monomers for gel dosimetry II: Dosimetric characterization of the ClearViewTM 3D dosimeter

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Abstract. ClearView is a colourless radiochromic 3D dosimeter that is chemically and mechanically stable before and after irradiation. Upon irradiation, colour is generated from the radiochemical reduction of a tetrazolium salt suspended within a gellan gum gel. Here we present the dosimetric characterization of small and large volume samples (4 mL and 1 L, respectively) from three different batches of ClearView. The dose sensitivity was linear up to 80 Gy and constant within a batch but varied among batches between 3.4×10^{-3} and 4.1×10^{-3} Gy⁻¹cm⁻¹. Once generated, the radiation signal within the large samples remained unchanged for at least 58 days. Both electrons and photons produced the same signal at different energy levels; however, at dose rates below 400 cGy/min, a drop in sensitivity was observed. Overall, ClearView is best suited for relative dosimetry up to 80 Gy at high dose rates.

1. Introduction

Modern radiotherapy relies on advanced techniques (beam modulation, arc delivery, etc.) to deliver high radiation doses to irregularly shaped, small volume targets [1]. At present, commissioning of equipment and quality assurance of treatments are most often performed by a combination of one- or twodimensional detectors, e.g. ion chambers, diode arrays and films [2]. However, these methods can provide only sparse three-dimensional (3D) data, which complicates the quality assurance process and adds uncertainty to its results [3]. To overcome this issue, the use of "true 3D" dosimetry has been proposed and multiple 3D dosimeters have been developed. These include gel, plastic and elastic (e.g. silicone-based) dosimeters with signal detection via magnetic resonance imaging or optical computed tomography [4]. Notwithstanding the wide variety of materials, true 3D dosimetry still has a limited clinical application, because of multiple drawbacks: poor chemical and/or image stability due to spontaneous colour change and/or signal diffusion within the dosimeter, complex and complicated preparation and use, imaging and data analysis.

The radiochromic gel discussed here was designed to provide chemically stable 3D dosimetry with no apparent signal diffusion. This allows dosimeter manufacturing, pre-irradiation and postirradiation imaging to be handled at an off-site facility, as a commercial product. The dosimeter is based on the radiochromic reduction of a colourless, water-soluble tetrazolium salt into an insoluble formazan dye suspended in gellan gum gel, as discussed in part I of this paper. The composition has been licensed to Modus QA (Modus Medical Devices Inc.) and developed as a product under the name ClearView.

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Here, the dosimetric characterization of ClearView gel in small (4mL) and large (1 L) volumes is presented.

2. Materials and Methods

2.1. Gel manufacturing

A 20-litre jacketed process reactor, described previously [5], was used for the manufacturing of 12 to 18-litre batches of ClearView with the following composition per litre: 12.50 g gellan gum (Alfa Aesar, USA, cat. no.: J63423), 103.60 g propylene glycol (AMRESCO, USA, cat. no.: 0575), 42.5 mg (0.10 mmol) 2,3-bis(4-nitrophenyl)-5-phenyl-2*H*-tetrazolium chloride (BNC) (Expert Synthesis Solutions, London, Canada) and deionized water. The gellan gum was dissolved at temperatures over 85 °C but the active ingredients were added at 70 °C. The hot solution was filtered through a 1.0 or 0.5 μ m filter and poured into one-litre clear polyethylene terephthalate jars. Controlled cooling allowed gel formation before storage at 4-6 °C. Simultaneously, poly(methyl methacrylate) (PMMA) cuvettes (1.0 cm square cross-section, 4 mL volume) were filled. The density of the gels at room temperature was determined with a 250-mL volumetric flask using three samples from two batches.

2.2. General set-up and irradiations

Optical measurements for the cuvettes were performed on a GENESYS 10S spectrophotometer (Thermo Fisher Scientific, Canada) at 535 nm, while the jars were imaged on a Vista 15 optical cone beam CT scanner with a green LED source (520-535 nm) (Modus QA, London, Canada). Irradiations took place within 2 to 5 days of preparation of the gels, which were pre-scanned on the day of irradiation, and post-scanned the following day with follow-up of up to 58 days. Irradiations were performed on either of two linear accelerators from Varian Medical Systems (USA): Clinac 21iX and TrueBeam at the London Regional Cancer Program (London, Canada). Cuvettes were placed three to six at a time on a PMMA block and submerged into water to a depth of 5 cm to the centre of the cuvette (for photons) or d_{max} (for electrons) and irradiated using 10x10 cm square beams. The 1-litre jars were irradiated using 6x6 cm square beams of photons or electrons, unless otherwise noted. The water surface over the cuvettes and the top surface of the gels were positioned at 100 cm source to surface distance. Percentage depth dose curves (PDD) were obtained as described elsewhere [6], and referenced to CC13 (IBA Dosimetry America, USA) ion chamber measurements.

To determine the linearity and stability of the dose response, cuvettes were irradiated up to 80 Gy at 600 cGy/min using 6 MV photons and 12 MeV electron beams. For the sensitivity in large samples, jars from three different batches were irradiated with 12MeV electrons to 40 Gy (at d_{max}) at 600 cGy/min [7]. The energy sensitivity to dose response was tested at 20 Gy, using 6 to 18 MV photons and 6 to 20 MeV electrons at 600 cGy/min in cuvettes from two different batches of gel. To test the sensitivity of the dose response to a wider range of energies and dose rates, cuvettes and jars of different batches were irradiated to 20 Gy at a range of electron and photon energies and dose rates, including flattening filter free (FFF) deliveries. Finally, a dose fractionation experiment was performed using arc treatments to 40 Gy at the isocenter using 6 MV photons at 600 cGy/min in two different settings: (i) in a single fraction, (ii) in five fractions of 8 Gy delivered sequentially.

3. Results and discussion

3.1. Physical characteristics

ClearView appears colourless or pink-tinted before irradiation and becomes purple upon irradiation. The gel is strong and inelastic at room temperature with a volumetric mass density of 1009 ± 1 g/L at 20 °C. The atomic composition (in mole percent) is 65.94% H, 31.35% O and 2.71% C.

3.2. Dosimetric characteristics

According to Figure 1A both photon and electron beams gave identical response in the cuvettes, while dose calibration in a jar showed lower but linear sensitivity. The decreased sensitivity in jars is likely due to the wider bandwidth of the LED source relative to the spectrophotometer used for the cuvette samples. The attenuation profile within the jar remained constant for at least 58 days, showing neither diffusion nor changing magnitude (Figure 1B), while both non-irradiated and irradiated cuvette samples remained stable for at least 21 days with noticeable drying of the gel thereafter (Figure 1C).



Figure 1. Calibration curves for cuvettes and a bulk sample at 600 cGy/min (A), stability of the background and dose response in a one-litre jar (B) and cuvette samples (C). Error bars show standard deviations for three cuvette samples.

Figure 2 shows the sensitivity and the PDD curves in jars from three different batches. Whereas the sensitivity remains linear in all cases, it varies between 3.4×10^{-3} and 4.1×10^{-3} Gy⁻¹cm⁻¹. The sensitivity variability can be attributed to two main factors: differences in the properties of the raw materials and changing process conditions. Here, the gellan gum used in the fabrication of the first batch (lot no. R13B050) had a different gel strength than the gellan gum used in batches 2 and 3 (lot no. Z22B034): 497 g/cm² and 606 g/cm², respectively, even though the supplier and catalog numbers were identical (Alfa Aesar, J63423). Further, the filtration process was updated between batches 2 and 3: from 1.0 to 0.5 µm filtration. Regardless of the different sensitivities, all tested batches showed consistent PDD curves, in agreement with the ion chamber measurements (Fig. 2B).



Figure 2. Batch-to-batch variability of sensitivity of three gel batches, irradiated to 40 Gy at d_{max} at 600 cGy/min by a 12 MeV electron beam: calibration curves (**A**) and PDD curves (**B**).

Figure 3 presents the dose response as a function of the beam energy and dose rate. No significant change of the sensitivity at different energies was seen in either electron or photon irradiations (Fig. 3A). Based

on the jar data, which is less noisy and more clinically relevant than the cuvette data, the sensitivity is constant within samples of the same batch at dose rate above 400 cGy/min. Additionally, the fractionation experiment showed identical responses in jars irradiated in a single fraction of 40 Gy (6 MV photons, 600 cGy/min) and in five consecutive fractions of 8 Gy (data not shown). However, at dose rates below 400 cGy/min the sensitivity dropped (Figure 3B).



Figure 3. Energy (**A**) and dose rate (**B**) effect on the dose response in cuvettes and jars from different batches. For direct comparison the data is normalized to the response of a 12 MeV electron beam irradiation at 600 cGy/mim. Error bars for cuvette data show standard deviations for three samples. Error bars for jar data show the error of the slope of the calibration curves.

We hypothesise that the decreased sensitivity below 400 cGy/min is associated with the low concentration of the active compound (BNC) in ClearView. Future research will focus on finding the mechanism of the dose rate effect with the goal of minimizing or eliminating it.

4. Conclusions

The ClearView radiochromic gel showed excellent stability for both irradiated and non-irradiated samples, without apparent optical changes or diffusion within a period of at least two months from manufacturing in large-volume samples. Batch-to-batch variability was observed in regards to the sensitivity to the delivered dose $(3.35 \times 10^{-3} \text{ and } 4.1 \times 10^{-3} \text{ Gy}^{-1} \text{cm}^{-1})$; however, the dose response was linear in all tested batches, identical for photons and electrons and unaffected by the energy in the range of 6 to 18 MV, and 6 to 20 MeV, respectively. However, there was a noticeable drop of the sensitivity at dose rates below 400 cGy/min. Thus, ClearView is best suited for relative dosimetry up to 80 Gy at high dose rates. Future research and product development will focus on minimizing the dose-rate effect and increasing the sensitivity of the ClearView gel.

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