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Effect of inorganic salts and glucose additives on dose–response, melting point and mass density of genipin gel dosimeters

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ABSTRACT

Genipin gel dosimeters are hydrogels infused with a radiation-sensitive material which yield dosimetric information in three dimensions (3D). The effect of inorganic salts and glucose on the visible absorption dose–response, melting points and mass density of genipin gel dosimeters has been experimentally evaluated using 6-MV LINAC photons. As a result, the addition of glucose with optimum concentration of 10% (w/w) was found to improve the thermal stability of the genipin gel and increase its melting point (T_m) by 6 °C accompanied by a slight decrease of dose–response. Furthermore, glucose helps to adjust the gel mass density to obtain the desired tissue-equivalent properties. A drop of T_m was observed when salts were used as additives. As the salt concentration increased, gel T_m decreased. The mass density and melting point of the genipin gel could be adjusted using different amounts of glucose that improved the genipin gel suitability for 3D dose measurements without introducing additional toxicity to the final gel.

Introduction

Genipin gel dosimeters are hydrogels infused with a radiation-sensitive material possessing the ability to yield dosimetric information in three dimensions [1]. Over the years, in addition to its use in herbal medicine, genipin has shown more potentially distinctive features, such as its biocompatibility and low cytotoxicity [2]. Genipin radiochromic gel has also exhibited considerable potential as a 3D dosimeter in advanced radiotherapy techniques. Several studies have investigated the characteristics and applications of genipin. Using Nuclear magnetic resonance (NMR) spectroscopy, Djerassi et al. [3] analyzed the chemical structure of genipin with molecular formula $C_{11}H_{14}O_5$. Genipin has also been cross-linked with amino acids to create stable cross-linked products with dark blue pigmentation [4].

Jordan [5] introduced the application of genipin gel as a 3D dosimeter and reported that genipin–gelatin combination presents an adequate response for absorbed doses up to 50 Gy. Subsequently, various research studies have been conducted to evaluate the application of genipin in radiotherapy applications. For example, Davies et al. [6] demonstrated that a genipin gel does not diffuse post-irradiation, which is a limiting feature of any gel dosimeter infused with radiation-sensitive species. Instead, the genipin hydrogel is bleached as a monotonic function of dose upon irradiation, and the color change can be optically quantified as an indication of absorbed dose, thereby facilitating the mapping of absorbed dose distribution in three dimensions with sufficient stability and sensitivity for doses up to 100 Gy. Furthermore, they asserted that the addition of sulfuric acid increases the sensitivity of genipin gel dosimeter for sufficient quality assurance of radiotherapy dosimetry. Gorjiara et al. [7] studied the water equivalency of genipin by characterizing its radiological properties. Their results indicate that genipin gel exhibits greater water equivalency in comparison with polymer gels and PRESAGE® formulation.

However, the material possesses a relatively low melting point of 25 °C [6] and requires a long time for scanning using magnetic resonance imaging. In addition, gel transportation makes genipin susceptible to flaccidity, so the 3D mapping recorded in the gel would be lost [8,9]. Therefore, this study hypothesizes that increasing the melting point or rigidity of genipin and adjusting its density with the addition of certain chemical components, such as glucose and inorganic salts, to its original recipe will improve the dosimetric properties of this dosimeter and maintain its dose sensitivity at an acceptable level. Recently, new polymer gel dosimeter made under normal atmospheric conditions based on less toxic monomers, such as 2-hydroxymethyl methacrylate (HEMA) with gellan gum as a gel matrix, has been proposed by Hiroki et al. [10], who optically assessed dose–response by determining absorbance. However, these prepared gelatin gels are limited because the gel possibly melts at relatively low temperatures, which would lead to the loss of 3D optical density information required for dose distribution.

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Jordan [5] proposed a new gel dosimeter based on gelatin cross-linked with genipin. A major component of the proposed dosimeter is genipin. Genipin is a fruit extract from *Gardenia jasminoides Ellis*. Genipin also serves as a cross link between proteins, such as gelatin, to form blue pigments [11,12]. Moreover, gelatin-derived bioadhesives demonstrate higher biocompatibility and less cytotoxicity when cross linked with genipin compared with other agents, such as formaldehyde and epoxy compounds [13–15].

According to Koeva et al. [16], N-isopropylacrylamide (NIPAM)-based gel produced using 10 wt% isopropanol exhibits approximately 1.6 times higher NMR dose sensitivity than a standard NIPAM-based gel, in spite of the same N,N′-methylene-bisacrylamide (Bis) concentration of 3 wt%. They also reported that the dose sensitivity of polyacrylamide-type gel increases as sucrose is added without increasing Bis concentration. In methacrylic acid-based gel dosimeters in which a cross linker is unnecessary, dose sensitivity increases as glucose is added [8]. They noted that dose sensitivity likely increases in gels with various water-soluble organic molecules (glycerol, isopropanol, sucrose, and glucose).

The presence of salts in gels influences rigidity and melting temperatures, which decrease as ion concentration in a solution increases [17]. Hayashi et al. [18] investigated the additive effect of various inorganic salts on the dose sensitivity of polyacrylamide based gel (PAGAT) and the methacrylic acid based gel (MAGAT) dosimeters; they found that the addition of some inorganic salts increases dose sensitivity. In contrast to an increase in dose sensitivity, a decrease in melting point can be attributed to the additives.

Sugars adjust the gelation properties of gelatin, thereby improving gel rigidity and increasing its melting point [19]. The addition of sucrose also enhances the dose sensitivity of gel dosimeters. Zhu et al. [8] added glucose to Methacrylic and Ascorbic acid in Gelatin Initiated by Copper (MAGIC gel) to modify its elemental composition, namely, Hydrogen, oxygen, carbon, and nitrogen; the new component improves the elemental composition of the gel to match with those of soft tissue and enhances the gel sensitivity and its melting point (increases by 5 °C). Healy et al. [20] explored the prospect of using glucose and sucrose additives in ferrous-agarose-xylenol orange (FAX) gel to enhance its optical sensitivity. Results of the study showed that FAX gel with glucose additive attained a maximum optical sensitivity increase of 55%. Davies et al. [6] reported that the original genipin gel starts melting at 25 °C, which is a relatively low temperature. Zhu et al. [8] claimed that the addition of glucose to the gel increased its melting point and stability for long image scan like MRI. As a result, the melting point (T_m) could be improved by varying glucose content in gel. Moreover, melting point in the gel dosimetry is also an important factor that influences its suitability for 3D dose measurements. Particularly, the 3D mapping recorded in the gel would be lost when the gel melted [8,9].

In the present study, a series of experiments and analyses have been conducted to investigate the effectiveness of these additives on genipin gel dosimetry. These additives were investigated for optimum visible absorption dose–response, melting points and density for 3D dose measurements.

Experimental procedure

Genipin gel preparation

Each genipin gel batch consists of gelatin type A (300 blooms (bloom is linked to mechanical elasticity of the gel and is used to classify gelatin types), G2500 (Sigma–Aldrich) and genipin (G4796, Sigma–Aldrich)). Ultrapure water (resistivity of 18 MΩ cm) produced from a Milli-Q system (Millipore, Bedford, MA., USA) was used in all experiments. Sulfuric acid (98%) was purchased from Merck (Darmstadt, Germany).

Based on a study carried out by Davies et al. [6], the typical composition in the final gel contains 50 mM genipin, 100 mM sulfuric acid, and 4% w/w gelatin. To optimize the dose–response and melting points of the genipin gel dosimeter, a suitable genipin gel formulation for dosimetry was investigated by varying the weight fractions of the gel ingredients, namely, genipin [25–125 μM], gelatin [2–7% w/w], and sulfuric acid [25–125 mM].

For all experiments, gels were prepared as follows: First, a sealed flask containing ultrapure water was placed in a water bath at 45 °C. Thereafter, the gelatin was added, and the solution was stirred with a magnetic bar until the gelatin was totally melted. Then, a clear solution was obtained. Afterward, genipin was added, and the water bath temperature was increased to 70 °C. The resultant mixture was stirred gently to prevent bubble formation in the gel for an additional 5 h. Sulfuric acid was subsequently added to the reaction flask, and the solution was stirred for another 10 min. Finally, the gel was poured directly into polymethyl-methacrylate (PMMA) standard cuvettes (Z188018, Sigma–Aldrich). The cuvettes were then capped with fit caps (9020, Starna), sealed from light, and stored at 4 °C for a minimum of 24 h before irradiation. To select the optimum gel composition, melting point, densities, water equivalency, and dose–response were investigated for each gel batch using suitable methods of evaluation.

Chemical additives

Using the optimum main composition of genipin gel, five batches were prepared, with one batch of the genipin gel formulated following the previously described procedure to serve as a control gel. For other gel batches, 0.5 and 1.0 M of magnesium chloride hexahydrate (M9272, Sigma–Aldrich) and potassium chloride (P 9541, Sigma–Aldrich) respectively were added prior to dissolving the gelatin and stirring for 10 min to obtain a homogeneous solution. Then, other steps of gel preparation and evaluation were performed in the same manner as described above. Rigidity, water equivalency, and optical dose–response were examined for each batch.

To adjust the elemental composition of the genipin gel, the genipin gel batches were modified by the addition of glucose, which was supplied by Merck (Darmstadt, Germany), as a carbon-rich ingredient to obtain a suitable melting point and mass density similar to soft tissue. One batch of the genipin gel was formulated following the previously described procedure as a control gel. The effects of adding glucose on radiation response and melting point of the genipin gel were investigated by varying the weight fractions of glucose in the gel batches. The weight fractions of glucose were varied between 5% and 15% of the total gel weight. Glucose was first dissolved in water, and then other gel components were added to the preparation flask via the same procedure described above. The dose–responses of the modified formulations were tested using 6-MV photon beam. Moreover, the densities and melting points of the new gel formulations were also measured.

For gel calibration, 30 cm × 30 cm slabs of Solid Water® phantom (RMI Gammex), presenting various thickness of 0.1 cm–5 cm, a density of 1.04 g/cm^3, and made from epoxy resins, were used. The phantom is designed to attenuate and scatter radiation in the same way as water, and fulfills the ICRU requirements for water equivalency in low- and high-energy systems [21,22].

Furthermore, water equivalent Perspex (PMMA) holders were designed with holes fitted to the cuvette size in each experiment to reduce the air effect. Cuvettes were placed in a 1.3 cm-thick Perspex holder, and then the holder was placed in a solid water phantom with 1 cm bolus placed both above and below the cuvettes to provide adequate build-up and scattering conditions. Furthermore, all phantom measurements were performed at room temperature ((23 ± 1) °C).

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