3D dosimetry fundamentals: gels and plastics

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Abstract. Many different materials have been developed for 3D radiation dosimetry since the Fricke gel dosimeter was first proposed in 1984. This paper is intended as an entry point into these materials where we provide an overview of the basic principles for the most explored materials. References to appropriate sources are provided such that the reader interested in more details can quickly find relevant information.

1. Introduction

The current use of hydrogels to measure 3D radiation dose distributions can be traced to the work of Gore et al. with a ferrous agarose system and magnetic resonance imaging (MRI) [1]. Radiochromic gels for chemical dosimetry of ionizing radiation were reported in 1951, but their 3D potential could not be exploited until digital computers and optical computed tomography were developed [2]. The key features of radiosensitive hydrogels for 3D dosimetry are their water or tissue equivalent response and their inherent 3D nature. The previous Dosgel proceedings contain a series of excellent reviews including several that focus on the chemistry of radiation sensitive hydrogels [3-7]. These reviews are the best starting point for studying gel dosimetry.

Two types of hydrogels have dominated the research: gels that contain monomers that undergo radical initiated polymerization due to absorbed dose and radiochromic hydrogels. The polymer gel dosimeters can be probed in 3D with MRI, ultrasound, x-ray and optical computed tomography (CT). While the radiochromic gels are usually read with optical CT to generate a full 3D dose distribution. Radiochromic plastics (Presage™) will be covered by other presenters at this meeting. Based on previous reports each of these materials has specific features that make them preferred for certain applications and it is anticipated that all will contribute to 3D dosimetry. Currently Presage™ (Heuris Pharma LLC, USA) and BANG (MGS Research, USA) are available for purchase and all other formulations require preparation by the users. Other considerations for material development for clinical usage include: ease of preparation and disposal, reproducibility of results, toxicity and raw material costs.

2. Water radiolysis

The water content of radiosensitive hydrogels ranges from 99% for ferrous agarose [1] and genipin gels to 80% for certain polymerization gel formulations [5]. The residual mass is predominantly organic materials such as gelatin and monomers. Dose deposition due to ionizing radiation is referred
to as water radiolysis. The text by Spinks and Woods [8] is a particularly important reference for radiation chemistry in general and the review by Appleby [3] at Dosgel’99 is a concise summary relative to hydrogels. In the case of megavoltage radiotherapy the majority of dose is deposited by collisions of high energy electrons with water molecules that initiate a cascade of chemical reactions. The relative concentrations of water radiolysis products are primarily determined by the presence of dissolved oxygen and the sample’s pH. The most important products are \( H_2O_2 \) and the radicals \( e_-^{aq}, H^+ \), and \( ^*OH \) in the absence of oxygen [9, 10]. Hydrogels prepared near room temperature and exposed to the air will contain approximately 1 mM of oxygen. In that case, new radicals such as \( ^*O_2^- \) and \( HO_2^* \) are formed while \( e_-^{aq}, H^+ \) are absent [9]. The water can be subdivided into a bound fraction and a free or bulk fraction. Bound and bulk water have thoroughly studied with NMR and in the specific case of hydrogels the review by Audet is recommended [11]. A direct link between the measured NMR characteristics of polymer gel dosimeters and theory was subsequently proposed [12]. Characterizing chemical reactions in the mixed bound-free water environment of hydrogels will provide insight for chemical gel dosimetry and model biological systems. For example, glycerol a common additive to gelatin hydrogels, stabilizes the collagen structure by enhancing the degree of bound water [13] resulting in stronger gels.

3. Hydrogels

The most common polymer gelling agents investigated for 3D dosimetry in hydrogels have been agarose (polysaccharide), gelatin (protein) and polyvinyl alcohol. Agarose gels are prepared at temperatures near 70°C. The elevated temperature has been problematic for many of the radiation chemistries that were investigated. For example, heating reduces the amount of dissolved oxygen and increases auto-oxidation rates [14]. This can lead to chemically nonuniform gels with unnecessarily elevated background levels for optical studies. In the case of ferrous-xylenol orange gels, the thermally increased autooxidation of ferrous ions during gel preparation produces dark gels before irradiation. Agarose gels are also translucent which minimizes their usefulness for 3D optical scanning. Gelatin is currently the most common gelling agent for preparing radiosensitive hydrogels. Hydrogel samples, with gelatin concentrations around 5% by mass, appear transparent and exhibit transmission levels in excess of 60% for 10 cm pathlengths will yellow or red light. If required, even transmission levels approaching 85% can be achieved by mechanical filtering of the gelatin solution or by the addition of refractive index matching materials such as sucrose or glycerol. Reducing scatter in gel translates into higher spatial resolution and greater dynamic range of optical measurements. For MRI and x-ray CT readout are likely insensitive to the inhomogeneities that cause optical scatter. The most common type of gelatin for hydrogels has been porcine, acid cured with a Bloom strength of 300. This gelatin type forms the stiffest gels. Depending on the formulation, gelatin gels typically melt between 28 and 34°C. In practice, if the gels are being handled in order to perform an irradiation experiment or transport to a readout instrument, temperatures exceeding 23°C may influence the gel uniformity. Crosslinking can provide radiosensitive hydrogels with melting points exceeding 60°C [15, 16]. However, crosslinking generally increases optical scatter and transverse magnetic relaxation rate as well. Gelatin can act either as a radiation sensitizer or desensitizer, depending on the radiochemistry under investigation [4, 6, 11, 16]. Polyvinyl alcohol (PVA) has also been investigated as a gelling agent. The initial interest in this synthetic polymer was due to the high purity, chemical simplicity, relative chemical inertness and low diffusion coefficients for ferrous xylenol orange gels. The high viscosity of PVA gels was problematic for preparation of large volume samples. Air bubbles became easily trapped when handling and became sources of nonuniformities, especially for optical readout. The scatter coefficients were also higher than analogous gelatin gels and continued to increase as the samples aged. For these reasons PVA gels have not been used for 3D dosimetry, but are quite helpful for investigating radiochemistries in hydrogels. Agarose, gelatin and PVA have all been sensitizers for ferrous and ferrous xylenol orange gels [17].
While gelatin has been useful, higher performance hydrogels with better optical and mechanical properties could be developed. For example, deformable gels would provide a unique solution to a relevant clinical issue, dose warping.

4. Fundamental principles of 3D dosimeters

4.1. Ferrous gel chemistry
Ferrous gels are based on adding gelling agents to the ferrous chemical dosimeter that is often referred to as the Fricke dosimeter. Gore et al demonstrated that 3D dose distributions could be recorded with ferrous gels and readout with MRI [1]. The chemistry of these gels was reviewed at the first gel dosimetry meeting, Dosgel’99 by [3, 18]. The dose sensitivity, tissue equivalence and 3D nature of these gels generated adequate interest in this specialty to generate this sequence of meetings dedicated to 3D dosimetry. However, materials with greater sensitivity and lower diffusion are required for routine clinical use. This need has generated many innovations in gel chemistry and readout technologies. These gels will continue to be important for fundamental radiochemistry studies but have been surpassed by many other radiosensitive gels.

4.2. Ferrous xylenol orange gel chemistry
The addition of xylenol orange to the Fricke solution allowed sensitive and reproducible detection of the ferric ions generated by absorbed dose with visible light. A thorough investigation of this innovation was conducted by Gupta and Nilekani [19]. Appleby first introduced xylenol orange into ferrous agarose gels [3]. However, due to optical scatter from the agarose hydrogel, effective optical scanning was limited to 2D slabs of gel [20]. The substitution of gelatin for agarose resulted in an effective transparent radiochromic hydrogel for 3D optical CT scanning [21]. FX gels have been the most widely studied radiochromic systems to date due to their ease of preparation and adequate dose sensitivity. However, subtle variations in dose responses have been reported between and within research groups. It had been surmised that the main variation was chemical purity of xylenol orange from different manufacturers. But, detailed dose fractionation studies concluded that several Fe(III)-xylenol orange species existed in equilibrium and that sampling at different wavelengths gave different dose responses [22]. FX gels continue to be investigated and are likely to be a standard for comparison of new gel chemistries. FX gels with lower diffusion rates and higher melting points are required.

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\text{Fe(III)}_1\text{X}_2 \ (480 \text{ nm}) \leftrightarrow \text{Fe(III)}_1\text{X}_1 \ (540 \text{ nm}) \leftrightarrow \text{Fe(III)}_2\text{X}_1 \ (590 \text{ nm}) \quad (1)
\]

4.3. Radiochromic micelle gels
Examining reviews of chemical dosimeters reveals that many are not water based [8, 23]. One approach to designing radiosensitive hydrogels is to form hydrid materials containing nonpolar nanodomains. The simplest approach involves identifying surfactants and reactants that are compatible with the formation of transparent hydrogels. This approach is general and is an active area of research on an industrial scale as society migrates from hydrocarbon solvents to “green chemical syntheses”. The initial reports have demonstrated that insoluble leuco dyes can be incorporated into gelatin hydrogels with nonionic surfactants [16, 24]. Diffusion measurements revealed that the more water soluble, cationic dye Malachite Green had a higher diffusion coefficient. This observation suggested that either uncharged dyes or ionic surfactants may form dye-micelle pairs leading to radiochromic gels with very low diffusion rates (Figure 1).
4.4. Radiochromic crosslinked gels
Genipin crosslinks gelatin to form a blue hydrogel. At low pH these gels are radiosensitive and the blue crosslinked gels fade with absorbed dose. This is another chemical approach to developing non-diffusing radiochromic hydrogels. The crosslinking provides stable gels with lower concentrations of gelatin (Figure 2). For example, 2% gelatin crosslinked genipin gels are stable at room temperature. The crosslinking also allows preparation of free standing gels that can be immersed in an acidic solution. These gels can be scanned optically, without interference of vessel walls and the gel response is uniform throughout allowing the potential for surface dosimetry as well [25]. The chemical simplicity of this system and the small amount of organic materials added, make this gel a candidate for reference water equivalent dosimetry. It may prove especially useful for 3D dosimetry at lower energies, for example with 100 kVp x-ray beams.

4.5. Radiochromic plastics
A promising material for routine clinical 3D dosimetry is the radiochromic plastic, Presage™ [26]. The host plastic is polyurethane and the radiochromic conversion of the colourless leucomalachite green to the dye malachite green is initiated by halogenated hydrocarbon free radicals. The system is robust and available for purchase, eliminating the need for a preparation laboratory. There has been a continuous improvement in optical quality and tissue equivalence from subsequent formulations (results to be presented at this meeting). High dose sensitivity, linearity and lack of diffusion are characteristics of this material.

4.6. Polymer gel dosimeters
Polymer gel dosimeters have been proposed in 1993 as materials that can integrate a radiation dose distribution in three dimensions [27]. Since their inception, many different variations on the gel composition have been tested and used. Fundamental processes influencing the radiation response of these materials have been unveiled, yielding a thorough understanding of the factors affecting the radiation dose sensitivity and stability, both spatial and temporal [12, 28-32]. In 2001, an antioxidant was added to the gel composition, which scavenged oxygen molecules present in the gel during manufacture under normal atmosphere [33]. A full understanding of the effect of antioxidants in gels is starting to emerge [33-35].
Figure 2. Schematic of radiochromic crosslinked gel matrix. Blue circles represent sites of crosslinking by genipin.

The main constituents of polymer gel dosimeters are water, monomers and a gelling agent. Traditionally, gelatin is used as the gelling agent and forms a three dimensional matrix into which the monomers are dispersed. Monomers are relatively small molecules that are characterized by a carbon-carbon double bond that can easily enter in a chemical reaction. Under irradiation, water radiolysis generates free radicals and molecular species; the former are highly reactive chemical species that can react with any gel constituent.

4.6.1. Polymerization process. Figure 3 provides a very simplified (and certainly non-exhaustive) schematic of the different chemical reactions that take place in a polymer gel dosimeter. When a water free radical reacts with a monomer, a process which is called “initiation”, a monomer radical is formed, which can react with another monomer, forming a polymer radical, and so on in a process called propagation. This is a crucial step where monomers react together, forming a polymer. Presence of this newly formed polymer modifies the physical properties of the dosimeter and different techniques can be used to probe these changes. A calculation based on reasonable assumptions suggested the number of monomer units in a polymer chain was roughly $10^4$ [12]. Termination of the polymerization reaction is also an important step since an absence of termination would result in full polymerization of the monomers after an insignificant radiation dose. Two polymer radicals can react together, a polymer radical can react with gelatin or with a water free radical; any of these will terminate the polymerization reaction. Oxygen is a very reactive chemical species that will rapidly react with water free radicals or with monomer radicals, efficiently inhibiting or terminating the polymerization reaction (figure 3). Preparing the dosimeter gel in an oxygen-free environment (i.e., a nitrogen-purged glove-box) can almost totally expel oxygen from the solution, at the expense of a more labour-intensive manufacturing process.

The polymerization process is rather fast in principle; that is when all constituents have easy access to other constituents. Certain monomers are hydrophobic (difficult to solubilize in water, for example
N,N’-methylene-bisacrylamide), which means their polymerization will yield a hydrophobic polymer. Access of other monomers becomes restricted and, as a consequence, the polymerization slowly propagates for hours.

4.6.2. Role of gelatin. So what is the role of gelatin in all this? Its main function is to provide a three dimensional matrix into which the polymer formed cannot diffuse, thus preserving the spatial integrity of the radiation dose distribution. However, the porosity of a gelatin matrix is such that small molecules [36], and perhaps also monomers, can almost freely diffuse. A direct consequence is that the radiation dose profile from a half-blocked field differs slightly from the expected “step” irradiation profile: a polymerization “overshoot” is observed at the edge of the field [37, 38]. This was interpreted as diffusion of monomers from the unirradiated region to the irradiated region and later confirmed by computer simulations [39]. However, gelatin is also known for its role as “scavenger” of water free radicals in acrylamide-based dosimeters [40]. As a result, higher concentration of gelatin leads to a decreased sensitivity since less water free radicals become available for reaction with

![Figure 3. Schematic representation of the interaction between different chemicals in a polymer gel dosimeter, more specifically for an acrylamide-based dosimeter in a deoxygenated environment.](image-url)
5. Conclusion
Many different materials are available for 3D dosimetry. Their usefulness is maximised when their composition and response is matched with the capabilities of a reading device [42]. A clear message is that there is not a single material that is universally optimized for every application and for every measurement device; materials and devices must be selected together for a given application.

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