Fundamentals of gel dosimeters

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Fundamentals of gel dosimeters

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Abstract. Fundamental chemical and physical phenomena that occur in Fricke gel dosimeters, polymer gel dosimeters, micelle gel dosimeters and genipin gel dosimeters are discussed. Fricke gel dosimeters are effective even though their radiation sensitivity depends on oxygen concentration. Oxygen contamination can cause severe problems in polymer gel dosimeters, even when THPC is used. Oxygen leakage must be prevented between manufacturing and irradiation of polymer gels, and internal calibration methods should be used so that contamination problems can be detected. Micelle gel dosimeters are promising due to their favourable diffusion properties. The introduction of micelles to gel dosimetry may open up new areas of dosimetry research wherein a range of water-insoluble radiochromic materials can be explored as reporter molecules.

1. Introduction

This article describes some of the fundamental chemical and physical phenomena that occur in three-dimensional (3D) gel dosimeters used for detection and verification of dose distributions used in cancer radiotherapy. The relationships between these phenomena and dosimeter performance are described. First, Fricke gel dosimeters are discussed, followed by polymer gel dosimeters and two emerging types of gel dosimeters (i.e., micelle gel dosimeters and genipin gel dosimeters). Only gel dosimeters containing water and a gelling agent are considered. Other dosimeters, such as plastic PRESAGE^{TM} dosimeters [1] are not discussed. This article focuses on recent work in gel dosimetry, which appeared in the literature since the previous 2010 IC3DDose conference.

2. Fricke gel dosimeters

Fricke or ferrous sulfate solutions, wherein the response to irradiation depends on the dose dependent transformation of ferrous (Fe^{2+}) ions into ferric (Fe^{3+}) ions, have been used to measure radiation doses for many years [2-4]. The initiation of modern 3D dosimetry is related to two important developments. The first development was the use of MRI to detect and quantify radiation-induced changes in Fricke solutions [5]. The second development was the spatial stabilization of dose information by dispersing Fricke solution throughout a gel matrix [6]. Unfortunatelly, the poor spatial stability of Fricke gels due to diffusion of Fe^{3+} ions constrains the permissible time between irradiation and measurements [7]. Limited success in reducing diffusion rates [8, 9] is obtained using different gelling agents (gelatin, agarose, sephadex and polyvinyl alcohol) and chelating agents such as xylenol orange, which induces colour changes that permit optical imaging [10-12].

Fricke gels are attractive for 3D dosimetry as they are easy to prepare, are radiologically tissue equivalent [13, 14] and give reproducible results [10]. However, like other popular gels used in dosimetry, Fricke gels are sensitive to conditions during preparation, irradiation and read-out (eg. impurities and temperature) [10]. The chemical yield (G value) of Fricke solutions is influenced by

oxygen (i.e., G= 15.5 ±0.2 ions/100 eV for a dosimeter in equilbrium with air and G= 8.2±0.3 for an oxygen-free dosimeter) [16-19]. Although Fricke gel dosimeters may seem to be simple at first glance, Monte Carlo simulations that predict the fundamental behaviour of Fricke solutions (without a gelling agent) account for more than 60 chemical reactions to simulate interactions between radiation and oxygenated water. Eleven or more additional reactions are required to account for interactions with SO_4^{2-} and Fe^{2+} [19-22]. Additional reactions would be required to account for interactions with gelatin and a chelating agent. As a result, Fricke gel dosimeters are not really that simple. This inherent level of complexity should be kept in mind when evaluating other potential 3D dosimeters.

3. Polymer gel dosimeters

Polymer gel dosimeters are the most widely used 3D gel dosimeters [23]. They contain water and gelatin, along with monomers and crosslinkers that polymerize in response to free radicals generated by water radiolysis [10]. The amount of crosslinked polymer that forms and precipitates at each location in the gel depends on the local radiation dose and the local concentration of monomer and crosslinker [24, 25]. Formation of tightly crosslinked polymer particles (microgels) induces changes in the physical properties of the dosimeter that can be detected using several imaging techniques (e.g., MRI, optical CT, x-ray CT and ultrasound scans) [26-35]. The radiation dose distribution can then be estimated from the resulting 3D images and used to verify the treatment plan that was applied [10].

A variety of different monomers and crosslinkers have been tested for use in polymer gel dosimeters [10, 36]. Polyacrylamide gel (PAG) dosimeters are the most studied because they have fewer problems with dose-rate sensitivity and temperature sensitivity than other polymer gel dosimeters. PAG dosimeters consist of acrylamide (Aam) monomer and N,N'-methylene-bisacrylamide (Bis) crosslinker (see figure 1) dissolved in an aqueous gelatin matrix. The main reactions that occur during free radical copolymerization of acrylamide and bisacrylamide are shown via a cartoon in figure 2. Although linear polyacrylamide is water-soluble, crosslinked polyacrylamide precipitates. The precipitated polymer is held in position by the gelatin matrix, preserving spatial information via a more effective means than in Fricke gel dosimeters. Although the precipitated polymer molecules cannot readily diffuse, the unreacted monomers can easily diffuse through the gel during and after irradiation. Consequently, inaccurate dosimetry results can be obtained in situations wherein polymer radicals persist over long periods of time and are able to react with the diffusing monomer and crosslinker (e.g., in anoxic PAG gels where radicals can persist for longer than 12 hours [37] and in low-dose rate brachytherapy applications where radicals are generated continuously for many weeks [38]. Note that all current polymer gel dosimeters face this same problem with diffusion of reporter molecules.

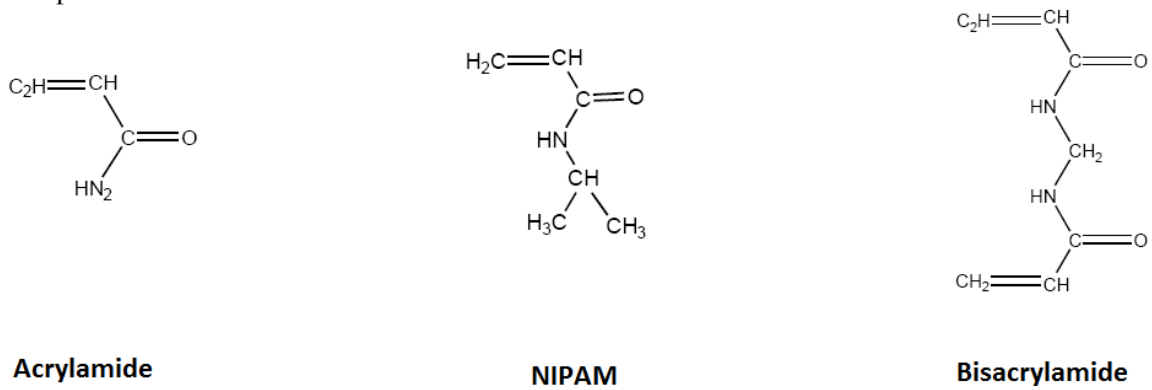

Figure 1: Chemical structure of acrylamide and n-isopropyl acrylamide (NIPAM) monomers and bisacrylamide crosslinker used in polymer gel dosimetry. Bisacrylamide is an effective crosslinker because two vinyl groups are available for polymerization.

In some recent dosimetry studies, acrylamide (which is a severe neurotoxin and suspected carcinogen) has been replaced with n-isopropyl acrylamide (NIPAM), shown in figure 1, which has lower toxicity than acrylamide and is less likely to be ingested via inhalation due to its lower volatility and is less able to pass through human skin [29, 39-48]. Note that proper safety precautions (i.e., preparation in a fume hood and use of gloves and goggles) still need to be used when manufacturing these dosimeters. NIPAM-based dosimeters have similar reaction chemistry as the PAG chemistry in figure 2, but seem to be more susceptible to pre-polymerization, which can result in cloudy phantoms prior to irradiation [39, 42].

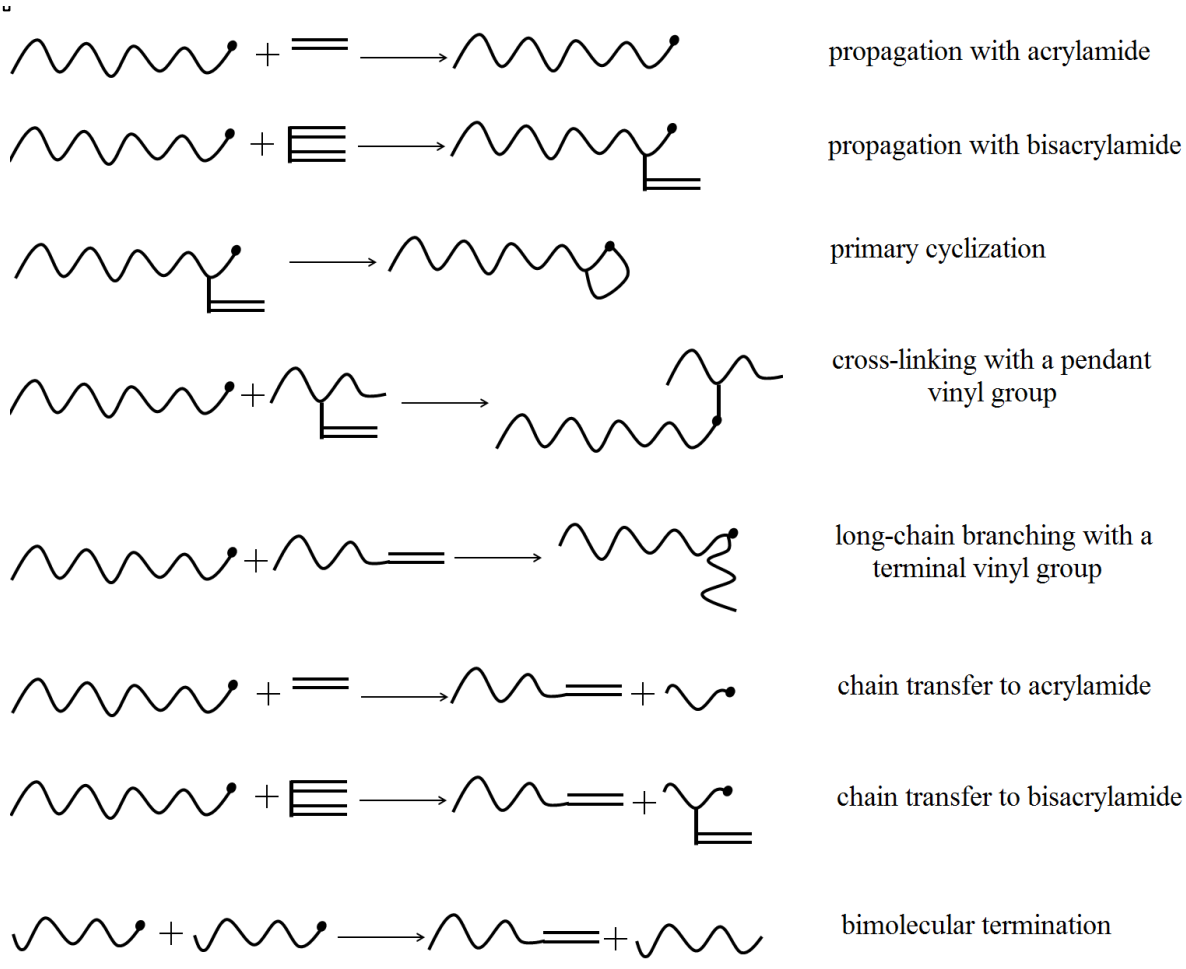

Figure 2: Main reactions in free radical copolymerization of acrylamide and bisacrylamide.

The sensitivity of PAG and NIPAM-based polymer gel dosimeters to radiation is directly related to %T, the total weight percent of monomer and crosslinker in the system [36, 37, 49], and to %C, the concentration of the crosslinker relative to the total monomer [37, 51]. Increases in both %T and crosslinker concentration tend to produce higher dose sensitivities, as measured by MR and x-ray CT [37, 40, 43, 49, 51-53]. The limited solubility of Bis crosslinker initially hampered the development of dosimeters with sufficiently high-dose sensitivities for accurate x-ray CT readout [54, 58]. Efforts to find effective crosslinkers with increased solubility were unsuccessful [59]. Recent NIPAM-based recipes with high %T have enabled additional bisacrylamide to be dissolved, resulting in polymer gel dosimeters with improved sensitivity and dose resolution for x-ray CT readout [41, 47, 48].

Measurement accuracy of PAG and NIPAM-based polymer gel dosimeters changes dramatically with %T and %C depending on the read-out technique used [60, 61]. For example, MRI techniques [62] can accurately measure dose distributions in PAG and NIPAM-based gels manufactured using traditional formulations that contains 6%T and 50 %C. However, cone beam optical imaging was complicated by light scattering when used to measure the dose distributions for such gels [26, 63, 64]. Reducing %T from 6 to 4 has improved the accuracy of cone beam optical measurements [26]. When using x-ray CT imaging, increasing %T to as high as 16 %, improves dose sensitivity and dose resolution [27]. It is clear that different recipes are suitable for use with different read-out techniques.

One of the major difficulties encountered by researchers when making polymer gel dosimeters is oxygen contamination [65-67]. Oxygen consumes primary free-radicals produced by water radiolysis and inhibits the growth of polymer radicals [68, 69]. Traditionally, PAG dosimeters were manufactured in oxygen-free glove boxes [67]. More recently, most polymer gel dosimeters are normoxic dosimeters that are manufactured in the presence of air and use an oxygen scavenger such as tetrakis hydroxymethyl phosphonium chloride (THPC) to remove oxygen that is initially dissolved in the gel solution [39, 70-73]. An additional benefit of using THPC in dosimeter recipes is that it helps to alleviate problems associated with long-lived radicals. Since THPC shortens the time period over which polymerization occurs, problems with edge enhancement are alleviated (i.e., there is a shorter time period when diffusing monomer and crosslinker can come in contact with polymer radicals). Unfortunately, THPC does not solve problems associated with oxygen that may leak into the phantom between manufacturing and irradiation [74, 75]. Minor oxygen leaks and interactions between this oxygen and THPC can cause severe dose inaccuracy [42, 76, 77]. Consequently, we recommend that internal calibration methods (e.g., based on depth dose) should be used instead of small calibration vials [29, 78-80]. Unexpected depth-dose behaviour will help to detect when oxygen has leaked into a phantom, so that results from contaminated phantoms can be discarded or used with caution.

4. Micelle gel dosimeters

Jordan and co-workers developed radiochromic micelle gel dosimeters for optical readout. The gel recipes consist of colourless leuco dyes (e.g., leuco malachite green or leuco crystal violet) emulsified in a hydrogel matrix using a surfactant [81, 82]. The leuco-dye molecules react with free radicals generated by water radiolysis, changing from colourless to deeply coloured as the radiation dose increases. Micelles are self-assembled aggregates of surfactant molecules that have both hydrophilic and hydrophobic parts. Above the critical micelle concentration (CMC), surfactant molecules orient themselves so that their hydrophobic parts repel away from surrounding water toward the centres of the micelles, leaving their hydrophilic parts in contact with water. The main purpose of using micelles in radiochromic micelle gel dosimeters is to emulsify the water-insoluble leuco-dye molecules within the hydrophobic core of the micelles to distribute the leuco dye throughout the 3D gel volume [82]. A second benefit is that micelles are significantly larger than individual leuco-dye molecules. As a result, the micelles, which contain the leuco dye, have low diffusivity within the gel matrix. Using emulsified leuco-dye molecules as reporter molecules results in improved spatial stability of dose information, compared with micelle-free optical dosimeters such as Fricke gel dosimeters and polymer gel dosimeters [81].

Current micelle gel dosimeters could benefit from further improvements as they are light sensitive and temperature sensitive during irradiation and tend to fade over time [82]. They also have relatively low dose sensitivity and may have significant dose-rate dependence [83]. One benefit of using micelles in 3D gel dosimeters is that, unlike traditional gel dosimeters, the reporter molecules do not need to be water soluble. In fact, very low or negligible water solubility will help to reduce diffusion and will improve spatial stability. Consequently, a range of new hydrophobic reporter molecules can be considered for use in 3D micelle gels. One type of water-insoluble reporter molecule that was recently studied is 10,12-pentacosadiynoic acid (PCDA) [81], which is the reporter molecule used in Gafchromic® films [85, 86]. PCDA changes colour in response to reaction with free radicals because it contains a diacetylene group (i.e., two carbon-carbon triple bonds separated by a carbon-carbon

single bond). When diacetylenes oligomerize in response to free radicals, they produce intense colour changes due to conjugated double and triple bonds [86-88]. Unfortunately, PCDA and two other diacetylenes were shown to be unsuitable for micelle gel dosimeters because they did not oligomerize within the micelles. Nevertheless, micelle gel dosimeters merit further study and development due to their diffusion properties and the range of new reporter molecules that can be considered.

5. Genipin gel dosimeters

A recent gel dosimeter containing genipin, gelatin and water is currently being studied for radiotherapy dosimetry applications. Genipin is a natural cross-linker of many types of hydrogel polymers, including gelatin [89-92]. During the cross-linking reaction of gelatin with genipin in aqueous media, the mixture slowly changes from colourless to deep blue. The melting point of the resulting gel is much higher than genipin-free gelatin gels [89]. The transparent blue gels bleach in response to irradiation and the colour change can be optically quantified [90]. Stable 3D dose information can be obtained shortly after irradiation [89]. Genipin gels respond linearly to radiation doses between 100 and 1000 Gy [90]. Lowering the pH using sulfuric acid increases dose sensitivity of genipin gels to doses between 0 and 100 Gy [90] so that these gels may be promising for 3D radiotherapy dosimetry in future.

6. Conclusions

Fricke gels are used because they are relatively simple and reproducible, even though they have significant problems with spatial stability due to diffusion. The chemistry of Fricke gels is actually quite complicated and involves a large number of chemical reactions. In addition, their sensitivity depends on oxygen concentration. The effectiveness of oxygen-dependent Fricke gels should be kept in mind when searching for new and improved gel dosimeter recipes.

Oxygen sensitivity is an important problem in polymer gel dosimeters, even when they are produced using THPC as an oxygen scavenger. As a result, great care should be taken to prevent oxygen leaks during the time between gel manufacture and irradiation. Otherwise, misleading results could be obtained. The use of internal gel calibration (i.e., using depth-dose information) rather than small vials is recommended as a means of detecting when oxygen contamination has occurred. Polymer gel dosimeters containing NIPAM rather than acrylamide are being developed and used because they are safer to make and use. However, even though NIPAM is less toxic and less likely to be ingested by skin absorption or inhalation, proper chemical safety precautions still need to be taken when it is used. NIPAM gels with high %T enable additional crosslinker to be dissolved, so that improved dose sensitivity and resolution can be obtained for use with x-ray CT read out. Lower %T recipes are better for use with MRI and optical scanning; different recipes should be used with different imaging techniques.

Micelle gels show promise due to their favourable diffusion properties and the range of new water-insoluble reporter molecules that might be considered. Genipin gels also warrant further investigation and development.

7. References

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