The chemistry and physics of polyacrylamide gel dosimeters: why they do and don’t work

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Abstract. Three factors that prohibit widespread clinical use of polyacrylamide gel (PAG) dosimeters are polymerization after irradiation ceases, formation of additional polymer near the edges of irradiated zones, and monomer toxicity. Polymerization can occur long after irradiation ceases because polymeric radicals cannot diffuse and terminate with other radicals. Small monomer molecules can diffuse toward trapped polymeric radicals and polymerize. Edge enhancement occurs because acrylamide and bisacrylamide diffuse from regions of high concentration (where the radical concentration is low) to adjacent regions where monomer concentration is low and the radical concentration is high. As monomers diffuse into the irradiated zone, they are polymerized by radicals near the edge. Acrylamide is a neurotoxin and suspected carcinogen that can be absorbed through the skin and inhaled, making it an undesirable monomer for polymer gel dosimetry. Less toxic monomers, such as n-vinyl formamide, should give similar dosimetry results, with less concern for safety. When selecting alternative monomers and cross-linkers for polymer gel dosimetry, it would be advantageous to choose larger molecules that diffuse more slowly, resulting in less edge enhancement. Larger molecules should also lead to improved safety, because they are less easily absorbed through the skin and are less easily vaporized and inhaled.

1. Introduction

Over the past decade, there has been considerable research into the use of polyacrylamide gel (PAG) dosimeters [1,2] for detecting and calibrating 3-D radiation dose distributions. In typical PAG dosimeters, a mixture of acrylamide, N,N’-methylene bisacrylamide, gelatin and water are irradiated using the desired radiation dose distribution. Water radiolysis [3] leads to the formation of free radicals, which initiate polymerization. Free radical copolymerization of acrylamide and bisacrylamide occurs by the mechanism shown in figure 1 [4]. Polymer chains grow by propagation reactions involving both acrylamide (which has one vinyl group) and bisacrylamide (which has two vinyl groups). Bisacrylamide tends to be consumed relatively more quickly [5,6] than acrylamide because of the extra vinyl group. When bisacrylamide is consumed by propagation, a pendant vinyl group (also called a pendant double bond) is created along the polymer chain. This vinyl group can subsequently react with a growing polymer chain to form a cross-link (reaction c), but most often it is consumed by primary cyclization (reaction b). The primary cyclization reaction is so favorable because it results in a convenient seven member ring [7]. An alternative cross-linker molecule with a greater distance between its vinyl groups could result in more crosslinks, using a smaller concentration of crosslinker. This may be an important consideration, because the amount of bisacrylamide that is
included in PAG recipes is very near to the water solubility limit of bisacrylamide. There is an opportunity to switch to alternative crosslinkers that would give more cross-links, which may lead to improved dosimeters.

As polymer chains grow and cross-link, they become insoluble and precipitate from the solution. The amount of polymer that precipitates and the cross-link density of the polymer chains influence water molecules that are dissolved within the precipitated polymer phase. As a result, the precipitated polymer, and the radiation dose that produced it, can be detected using NMR or magnetic resonance imaging [1,2]. Growth of a polymer chain can be halted by a chain-transfer reaction (reaction e), resulting in a dead polymer molecule and a new growing polymer chain, or by termination with another free radical (reaction f), leading to destruction of the free radicals. Jirasek and Duzenli5 have shown that an increase in the concentration of gelatin in the PAG recipe reduces the rate of monomer consumption, suggesting that the growing polymer chains can react with gelatin, producing gelatin radicals that are slow to reinitiate polymerization [8].

Several problems prohibit the use of PAG dosimetry for widespread clinical use. These include (i) long-lived radicals that result in continued polymerization after irradiation ceases [9], (ii) edge enhancement, wherein extra polymer forms near the edge of zones where the radiation dose is high, and (iii) monomer toxicity. Problems (i) and (ii) are physical and chemical problems that result in inaccurate dose calibration, whereas problem (iii) is a more serious biological and human problem that will influence how polymer gel dosimeters are handled and disposed of, and whether they are safe to use in a clinical setting. Recent work [8,10] on mathematical modeling of PAG dosimeters has helped us to study problems (i) and (ii) and should provide guidance for selecting safer monomers that will be suitable for gel dosimetry applications.

![Figure 1](image)

**Figure 1.** Free radical copolymerization mechanism for acrylamide and bisacrylamide.

**2. Problems with PAG dosimetry**

**2.1. Long-lived radicals**

In simple free-radical solution polymerization systems (those without cross-linking, branching or precipitation), growing polymer molecules readily diffuse through the reaction medium, encounter other free radicals, and terminate. When new radicals are no longer being generated, the rate of polymerization quickly falls to zero because there are no longer any free radicals. However in PAG dosimeters and other systems in which immobile cross-linked polymer molecules form, reduced
mobility of radicals leads to slower termination reactions and higher polymerization rates [11,12]. Termination is inhibited because it is difficult for trapped polymeric free radicals to diffuse through the solution to encounter other radicals. Propagation continues because monomer molecules, which are much smaller and more mobile than the growing polymer chains, can diffuse through the reaction mixture to encounter the radicals. Each polymeric radical continues to grow until either: the radical reacts with a monomer by chain transfer producing a new free radical that will initiate further propagation, the polymeric radical eventually encounters another radical and terminates, the radical reacts with an inhibitor such as gelatin or an impurity (e.g. oxygen) producing a new radical that may not be sufficiently energetic to initiate polymerization [13,14], or all of the monomer is consumed.

It is important to used well controlled sample handling techniques that limit post-irradiation polymerization. Possible approaches include: (1) storing the irradiated dosimeter at a low temperature to reduce the rate of polymerization while awaiting imaging, because lower temperatures lead to lower polymerization rates and (2) exposing the dosimeter to oxygen after irradiation is complete because oxygen retards polymerization and (3) ensuring that imaging is done at a controlled time after the irradiation.

2.3. Edge enhancement

In PAG dosimeters, a thermodynamic driving force encourages diffusion of polymer and the monomers from regions of high concentration to low concentration. Diffusion of polymer molecules (both the dead polymer and the growing polymer) occurs at a very low rate, because movement of the polymer is severely inhibited by the large size of these molecules and by entanglement with gelatin. In PAG dosimeters, diffusion of the polymer is so slow that the primary mode of diffusion is reaction diffusion [8,10,15], in which the radical end of the polymeric chains move slowly through the solution as new acrylamide and bisacrylamide units add to the growing polymer molecules. This is a much slower process than the centre-of-mass diffusion of acrylamide and bisacrylamide molecules, which are much smaller and can diffuse freely within the gelatin matrix.

We have used a mathematical model to investigate polymerization and diffusion within a PAG dosimeter in which a portion of the vessel is irradiated uniformly and the remainder is not irradiated [10]. Simulations indicate that almost no polymer forms beyond the edge of the irradiated zone, due to the very limited ability of the polymer to diffuse. However, substantial amounts of additional polymer form just inside of the edge of the irradiated zone, due to diffusion and subsequent reaction of acrylamide and bisacrylamide molecules that were originally in the non-irradiated zone. The amount of excess polymer near the edge increases with increasing absorbed dose, using a fixed dose rate. Also the amount of additional polymer near the edge increases as the time post-irradiation increases. Unfortunately, this extra polymer will result in false information about the radiation dose that was applied near the edge. Several approaches that could help to reduce edge enhancement are: (i) use of larger monomer and cross-linker molecules that will diffuse less freely through the gelatin and water solution during irradiation and (ii) the methods described above for reducing the effects of long-lived radicals, because these long-lived radicals lead to additional edge enhancement during dosimeter storage after irradiation ceases.

2.3. Monomer toxicity

Perhaps the main impediment to clinical use of PAG dosimeters is the extreme toxicity of acrylamide. Acrylamide is a severe neurotoxin, as well as a suspected human carcinogen and a teratogen. It is readily absorbed through both the skin and the respiratory tract [16]. Bisacrylamide, a larger molecule that is not as readily absorbed through the skin or vaporized into the air, is a suspected mutagen and teratogen, but is not nearly as dangerous as acrylamide [17]. After acrylamide and bisacrylamide are polymerized, the polymer is safe to handle and use, as long as there is no residual unreacted monomer. However, the objective of PAG dosimetry is to polymerize and cross-link acrylamide and
bisacrylamide where the radiation dose is high, and leave them as unreacted monomers in regions where there is no radiation. As a result, PAG dosimeters contain substantial amounts of unreacted monomers and are dangerous products to make, handle and dispose of.

Acrylamide (and acrylamide crosslinked with bisacrylamide) is used industrially to make flocculants, thickeners, hydraulic friction reducing agents and sorbents, because polyacrylamide and its derivative polymers have good properties for these applications, and acrylamide and polyacrylamide can be produced cheaply at large scale [18,19]. Companies who make water soluble and water-swellable polymers for commercial purposes are switching away from acrylamide to other less toxic monomers to avoid exposing their workers and the environment to acrylamide. One monomer that is being using instead is n-vinyl formamide [18-20] (shown in figure 2). N-vinyl formamide, which is an isomer of acrylamide, is a liquid at room temperature. Like acrylamide, it is soluble in water and is readily polymerized using free radicals. N-vinyl formamide must be used with care because it is damaging to the eyes and is a suspected teratogen, but it is much safer to use than acrylamide. A difficult problem faced by industrial users of n-vinyl formamide is that, during polymerization, a side reaction can cause n-vinyl formamide to cross-link and precipitate from solution [18,19]. The presence of this insoluble polymer (referred to as gel) is undesirable in most applications. Fortunately, these cross-linking reactions should not be a problem for polymer gel dosimeter applications, but they might influence how much cross-linker is purposely included in the recipe. Since n-vinyl formamide is similar in size to acrylamide, it will likely not help in reducing edge enhancement.

![Chemical structures of acrylamide and n-vinyl formamide.](image)

**Figure 2.** Chemical structures of acrylamide and n-vinyl formamide.

### 3. Summary and future work

A variety of chemical and physical phenomena influence the amount of polymer that forms, cross-links, and precipitates in PAG dosimeters. Copolymerization of acrylamide and bisacrylamide is more complicated than standard free radical polymerization, due to cross-linking and primary cyclization reactions, and to precipitation of the cross-linked polymers. Inability of the cross-linked polymer molecules to diffuse within the water and gelatin matrix ensures that information about the spatial radiation dose distribution is not lost. Unfortunately, these same low diffusion rates for polymeric radicals result in long-lived radicals that persist long after irradiation, resulting in inaccurate dose information. Edge enhancement results from diffusion of monomers from regions of low radical concentration into adjacent regions of high radical concentration, and subsequent polymerization. Edge enhancement becomes worse as the time post-irradiation increases, giving more time for monomers to diffuse into the irradiated zone. There is no good way to stop edge enhancement, but it
could be greatly reduced by selecting monomer and cross-linker molecules that are larger and diffuse more slowly. Since acrylamide is highly toxic, alternative monomers need to be adopted so that physicists and their coworkers won’t be exposed to a dangerous neurotoxin. Industrial producers of water soluble and swellable polymers, who are searching for safer monomers to make their products, need to be concerned about both the price and large-scale availability of each potential monomer. Medical physicists need not be so concerned about these factors, so a much broader range of monomers are available for consideration. Future work will involve identifying suitable monomers and crosslinkers that are water-soluble and available in kilogram quantities, which will be safer to use than acrylamide and bisacrylamide, and will diffuse more slowly, resulting in less edge enhancement and post-irradiation polymerization.

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