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Review Article

Three-dimensional dosimeter: Past until future

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Abstract: In radiation therapy, an accurate dose measurement and a precise dose delivery to the tumor are directly associated with better treatment outcomes in terms of higher tumor control and lower post radiation therapy complications. Recently, gel dosimetry was developed into a powerful tool for radiotherapy treatment verification and quality assurance. This review summarizes development of gel dosimeter models through improvement in their sensitivity and uniformity as three- dimensional detectors. The most important characteristics as well as the limitations that can affect the performance of the gel dosimetry systems have been explained. An outline of both clinical and research contemporary applications is given particularly emphasizing new applications like brachytherapy, diagnostic radiology and radiobiological experiments. Review concludes through an overview of future directions in development of this important dosimetric tool revolving.
Keywords: dosimeter, gel dosimetry, radiotherapy treatment, 3D dosimetry.

History of Three-dimensional dosimetry:

Three-dimensional dosimetry can be performed in two ways: 1- Automated water phantom, in which the, sensor either ion chamber or solid-state diode move automatically and dose distribution is measured in water tank, but the accurate dose measurement in complicated dose distribution is not possible. 2- Film dosimetry; in which dosimetry of complicated shapes is possible however, the film dosimetry is basically a two-dimensional dosimetry technique. Three- dimensional dosimetry is possible only with spatial combinations of the films. With introducing gel as a dosimeter, a new revolution in 3D dosimetry is happening. Since the gel used for dosimetry contains more than 99% of water therefore it can be considered as tissue equivalent. Two types of gels have been used, Fricke and polymer gels. In Fricke gel the Fe2+ ions oxidize to Fe+3 ions due to ionization (Gore et al. 1984[1], Olson et al [2]. 1990 and Tarte et al. 1996[3]).

Polymer systems for the use of radiation dosimetry were first proposed as early as 1954, where Alexander et al. discussed the effects of ionising radiation on polymethylmethacrylate [4]. Following this, Hoecker and Watkins [5] in 1958 investigated the dosimetry of radiation-induced polymerization in liquids, and in 1961, Boni [6] used polyacrylamide as a gamma dosimeter. In 1992, a polymer formulation was suggested that consisted of acrylamide (AA) and N, N0-methy-lene-bis-acrylamide (bis) monomers infused in an aqueous agarose matrix. This polymer gel formulation did not have the diffusion limitations of Fricke gels [7]. In 1994, Maryanski et al. modified the formulation by replacing agarose with gelatin and named the, now commercial, product BANG gel [8]. A procedure for manufacturing what is now commonly referred to in the literature as PAG, an acronym for polyacrylamide gel, was later described [9]. Upon exposure of the radiological tissue equivalent [10] PAG dosimeter to radiation, polymerization of the co-monomers is induced by the free radical products of water radiolysis resulting in a 3D insoluble polymer network infused within the gel matrix. Since the extent of the resulting polymer structure is a function of dose, MRI can be used to evaluate the relaxation rates which can be related to dose by means of an R2 (1/T2) versus dose calibration curve. The polymerization in the irradiated PAG is known to be inhibited by oxygen and therefore, requires that the polymer gel be produced in an oxygen free or hypoxic environment [9]. Over the years many formulations of polymer gels have been published [11-13] demonstrating its use mainly in radiotherapy dosimetry [14-17]. In 2001, a method was described for developing polymer gels in an oxygen or normoxic environment. The formulation became known as MAGIC polymer gel which is an acronym for Methacrylic acid (MAA), Ascorbic acid (AscA), Gelatin, Initiated by Copper [18]. The addition of the AscA oxygen scavenger into the formulation resulted in one of the major limitations of polymer gel dosimeters being overcome, allowing the polymer gel to be manufactured under normal atmospheric conditions upon the bench top. De Deene et al. investigated the

various components of the original MAGIC polymer gel formulation and proposed some alternative oxygen scavengers, in particular tetrakis (hydroxymethyl) phosphonium chloride (THPC), which was originally proposed in 1996 by Billingham [19] and from which MAGAT polymer gel was developed [20, 21]. Further formulations were also proposed such as MAGAS and PAGAS [20, 21] for which radiological tissue equivalence was investigated [22]. In 2005, Venning et al. investigated a normoxic formulation based on the original hypoxic PAG polymer gel formulation of AA and bis dissolved in a gel matrix with the novel addition of THPC and hydroquinone (HQ). This formulation was given the acronym PAGAT polymer gel [10]. PAGAT polymer gel was subsequently shown to be useful for both radiotherapy and diagnostic dosimetry with high spatial resolution being achieved when imaged with MRI in the relevant clinical dose ranges [17].

Author and date	**Type of gels**	**Composition**	**Principal finding**
Day and Stein, 1949 [23]	Aqueous solution	Aqueous solution + 'acceptor' (e.g. benzene/ sodium benzoate/	Aqueous solution irradiated with ionizing radiation would produce hydrogen and hydroxyl radicals that will chemically react with 'acceptor' that can be use as a measure of radiation dose
Day and Stein, 1950 [24]	Gels dosimeter	Gelatine/agar + dye (e.g.methylene blue/ phenolindo-2)	Gels change color in the function of radiation dose
Alexander et al, 1954 [25]	Solid polymer	Polymethylmethacrylate	Effects of ionizing radiation can be measured by viscosity measurement of irradiated solid polymethylmethacrylate
Andrew et al,1957 [26]	Agar gels	Chloral hydrate agar gel	Investigated depth doses for x-rays and electrons using spectrophotometry and pH probe measurements
Hoecker and Watkins, 1958 [5]	Polymer liquid/gel	Polymerizable liquid in gelatin capsules	Investigated the degree to which a liquid monomer solution became solid through polymerisation due to radiation.
Boni et al,1961 [6]	Polymer gel	Polyacrylamide in polystyrene and glass vials	Used polyacrylamide gel as gamma dosimeter
Gore et al, 1984 [1]	Gels dosimeter	Ferrous sulfate chemical (Fricke Gels)	Chemical changes in gels due to irradiation can be measured by nuclear magnetic resonance imaging(MRI)
Kennan et al,1992 [27]	Aqueous solution	N,N'-methylene –bisacrylamide and agarose	Study the NMR longitudinal relaxation which showed that the relaxation rate increased with absorbed dose
Maryanski et al, 1993 [28]	Polymer gel	BIS, Acrylamide, nitrous oxide and agarose (BANANA)	Proposed new formulation of polymer gel based on polymerization of monomer (Acrylamide and BIS monomers infused in agarose matrix)
Maryanski et al, 1994a,b [29,8]	Polymer gel	BIS, Acrylamide, nitrogen and gelatine	New formulation of polymer gels were

		(BANG)	introduced by replacing agarose with gelatin
Baldock et al, 1998a [9]	Polymer gel	Gelatine, Acrylamide, BIS (PAG)	Introduce simple and inexpensive method to fabricate polyacrylamide gel.
Pappas et al,1999 [30]	Polymer gel	N-Vinylpyrrolidone, BIS, Gelatine	Developed different composition of polymer gel based on NVinylpyrrolidone
Lepage et al, 2001a [31]	Polymer gel	Acrylamide/acrylic acid/ methacrylic acid/ 1-vynil-2-pyrrolidinone/ 2-hydroxyethyl methacrylate/ 2-hydroxyethyl acrylate, gelatin/ agarose, BIS	Study of different formulations of polymer gel using different types of monomers.
Fong et al, 2001 [18]	Normoxic polymer gel	Methacrylic acid, gelatine, hydroquinone, copper sulphate, ascorbic acid (MAGIC)	Developed normoxic type of gels
De Deene et al, 2002a [21]	Normoxic polymer gel	Gelatin, Methacrylic acid/ Acrylamide ascorbic acid/copper (II) Sulphate/THP/N-acetylcysteine hydroquinone, BIS	Study of different chemical components of normoxic gels. THP was found to be the most reactive antioxidant.
Adamovics J et al, 2003 [32]	radiochromic gel	***1.1.*** *Polyurethane material doped with leucodyes (PRESAGE ™)*	Detecting and displaying a dose or doses of penetrating radiation by forming within the polymeric matrix a 3D dosimetric map which is measurable and quantifiable by various known procedures.
Zahmatkesh et al,2004 [33]	Normoxic polymer gel	Methacrylic acid, gelatine, hydroquinone, copper sulphate, ascorbic acid,agarose (MAGICA)	Developed normoxic type of gels
Fernandes et al, 2008 [34]	Normoxic polymer gel	***1.2.*** *Methacrylic acid, gelatine, hydroquinone, copper sulphate, ascorbic acid, Formaldehyde (MAGIC-f)*	Developed normoxic type of gels

Many publications on different compositions and formulations of polymer gels are available ([35 - 36]). Numerous studies have also been conducted on potential clinical applications of polymer gels especially using normoxic type gel dosimeter [37]. So this paper we are review of history, application and problem of 3-D dosimetry on medical science.

Three- dimensional dosimeters methodology:

Polymer gel dosimetry involves three steps: first, the radiation sensitive polymer gel is fabricated and poured into an antropomorphically shaped container and associated calibration vials, and left to set. Second, the antropomorphic phantom and associated vials are irradiated. Third, after polymerization the gel is scanned by use of a dedicated optimized imaging technique, and the acquired images are subsequently analyzed.

Essential characteristic of 3.D dosimeters:

Effects of Oxygen:

The process of polymerization is initiated by free radicals formed from the radiolysis of water in the gel composition. These free radicals combine with the monomers making them reactive. Molecular oxygen, however, acts as a scavenger of these free radicals and

hence prevents them from initiating the polymerization process [38]. Even trace amounts of oxygen in the gel mixture can lead to the failure of the gel as an effective dosimeter. An important component of the manufacture of polymer gel dosimeters is the removal of oxygen from either a reaction flask or a glove box by the bubbling of an inert gas, for example nitrogen or argon, through the water that is to be used in the formulation before mixing the other ingredients [39]. It is, therefore, important to ensure the type and quality of the seals used on the vessels do not allow the diffusion of oxygen into the vessel. Maintaining a strict hypoxic environment has been a significant drawback of polymer gel dosimeters in the past and made the process of polymer gel dosimetry awkward to implement into clinical practice.

However, with the advent of normoxic polymer gel dosimeters, as described above, the strict hypoxic environment is no longer required. Normoxic polymer gel dosimeters can be manufactured under normal atmospheric conditions on the bench top. However, the development of normoxic polymer gel dosimeters is in their infancy and much work is still to be done to be able to fully understand and integrate normoxic polymer gel dosimeters into clinical practice.

Effect of Light:

The initiation of the polymerization process should be caused by the radiolysis of water that leads to the production of free radicals, as discussed above. However, a number of alternative initiators exist. Bright light, especially sunlight, can initiate photopolymerisation of the gel before it is irradiated and consequently degrade the sensitivity of the gel [38]. Polymer gel dosimeters should, therefore, be manufactured, irradiated and stored away from strong light sources.

Temperature:

There are several places where temperature plays a significant role in the manufacture of the gel. The first step in the manufacturing procedure requires high temperature to facilitate mixing of the gelatin and water. The gelatin must be added whilst the water is at room temperature to avoid the gelatin forming lumps. Once the gelatin has soaked into the water, the mixture is then heated to ~50 °C to ensure that the gelatin has completely dissolved into the water. The temperature of the mixture must be kept below 55°C when mixing the monomers to avoid prepolymerisation that may be caused due to the temperature of the solution. Following the manufacture, the temperature of the gel should be kept low to ensure the gel sets in the vessel it has been placed in. Salomons et al. (2002) have showed that a temperature increase occurs within a polyacrylamide gel dosimeter during and immediately after irradiation due to the exothermic polymerization reactions. This temperature change can affect polymerization reactions within the gel dosimeter and hence may lead to inaccurate calibration of gel dosimeter images. In order to minimize the effect of this artifact on the dose maps produced by gel dosimeters, the size, shape and temperature of the gel dosimeters must be controlled.

During magnetic resonance imaging, the temperature of the polymer gel has a very significant effect of the overall R2-dose sensitivity of the polymer gel dosimeter. Several authors have found an increase in the R2-dose sensitivity of the gel as temperature decreases. This effect is thought due to a change in the proton exchange rates in the gel as the temperature is varied. As the temperature is decreased, the motion of the water protons becomes slower. This increases the exchange rate of energy between protons [38]. It has also been found that a change of even 1°C within a phantom can give rise to dose uncertainties of approximately 50 cGy in dose maps derived from gel dosimeters imaged using MRI . The temperature of a gel undergoing the imaging process must be kept constant to avoid changes in the relaxation rates over the time of imaging. The gel should be kept in temperature controlled conditions, such as those of the MRI room, for at least 12 hours before imaging to allow time for the dosimeter to equilibrate to the scanning temperature.

Concentration of Monomers:

The R2-dose sensitivity of a gel may be increased by increasing the total monomer content of the gel, typically symbolized using %T. The typical concentrations of monomers range from 3 % to 9 % of the total weight. An increase in the monomer concentration is limited, though, by the low solubility of the bis and crystallization of the gel that can occur during storage. Also, as some monomers used in polymer gel dosimetry may be strong acids, high concentrations can adversely affect the gelatin within the gel dosimeter over time. In order to produce the highest R2-dose sensitivity, the relative proportion of each of the individual co-monomers, typically symbolized using %C was found to be 50 % of the total monomer content [40]. This result was supported by investigating the effect of chemical exchange on magnetization transfer in polyacrylamide gels.

Ageing of the Gel:

Unlike the problems encountered by Fricke gels where there is a diffusion of the ferric ions over time thus degrading the spatial information contained in the gel dosimeter, polymer gel dosimeters are not as limited by time constraints. One exception is a time evolution of the dose response that occurs following the irradiation of the gel as polymerisation processes are occurring at the greatest rate and may lead to errors in the use of separate calibration vials and phantom [38]. De Deene et al., in an investigation into the stability of the polymer gel dosimeter structure, found that the initial 12 hours post-irradiation yield significant errors

due to the chemical instability of the polymer gel [41]. After around 12 hours, most polymer gel dosimeters maintain a reasonable temporal stability over a period of several days.

Measurement dose absorption in Three- dimensional dosimeters:

Since the work of Gore et al in 1984 [1], the majority of investigations have been undertaken with MRI. However, in 1996 Gore et al and Maryanski et al demonstrated the potential of optical-CT as an alternative imaging technique to MRI for PAG-type polymer gel dosimeters [42-43]. This technique was further investigated by Oldham et al [44-46]. In 2000 Hilts et al demonstrated the use of X-ray CT to image PAG-type gels and subsequently used X-ray CT to investigate stereotactic dose distributions [47]. In 1998 Baldock demonstrated the use of variational spectroscopy to evaluate PAG-type polymer gel dosimeters [48- 49] and in 2002 Mather et al demonstrated the use of ultrasound to image polymer gel dosimeters [50].

A new class of polymer dosimeter, PRESAGETM (Heuris Pharma, Skillman, NJ) [51] was proposed and based on clear polyurethane combined with leuco-dye leucomalachite green. The components of the dosimeter, which was subsequently patented in 2006 [52], include an alkyl diisocyanate pre-polymer, a hydroxyl reactive polyol along with a catalyst, which polymerises into optically clear polyurethane. Although not suitable for MRI evaluation, this radiation tissue-equivalent dosimeter [53] contains leuco dyes which have a maximum absorbance at a wavelength of 633 nm and are therefore suitable for evaluation with a He-Ne laser-based optical scanning system [54-56].

Applications and limitations of polymer gels:

Polymer gels have been used for basic dosimetry including dose distributions, determination of internal dosimetry and evaluation of tissue heterogeneity for various clinical applications [37]. The ability to record doses in 3D makes polymer gels the attractive dosimetric tool to measure and verify dose distribution. Polymer gels have been used to verify dose distribution in phantoms obtained with treatment planning in conformal radiotherapy [57]. They have also been proven to be employed for IMRT treatment verification and regular QA [58-59]. As 3D dosimeters, polymer gels are very useful for visualization of steep dose gradient and dose distribution in high and low dose brachytherapy source [60]. Polymer gels have also been successfully applied for measurement of 3D dose distributions of proton beams [61-62] and heavy ion beams [63]. Farajollahi et al (2000) used polymer gels for boron neutron capture therapy and observed an increase in dose response in a PAG doped with boron as compared to an un-doped PAG [64]. This study showed that polymer gels can also be doped with other elements or chemicals such as boron. Experiments have also been undertaken
to investigate the dosimetry of unsealed therapy radio nuclides I-131 [65-66] and P-32 [67]. This wide scale of applications is due to the dosimetric properties of polymer gels; their stability, spatial integrity, temperature insensitivity, dose rate, energy dependence and tissue equivalence [37]. However, there are some limitations of polymer gels which must be taken into account whenever they are employed. Gel experiments are time consuming since the whole process of fabrication, irradiation and scanning requires a minimum of 45 hours to complete [37]. Oxygen contamination also is considered to be a significant issue in polymer gel dosimetry. Precautions must be taken, such as the use of well sealed glass or Barex vials, and experimental protocol must be observed in order to avoid oxygen contamination to the gels. Experimental parameters such as temperature, dose rate and scanning parameters must also be controlled and optimized to ensure less uncertainty as well as reproducible and reliable results.

Dose enhancement measurement using polymer gel:

Polymer gel dosimeters are a type of radiation dosimeter used in medical radiation therapy that are able to directly measure the effects of contrast agents or metallic radiation dose enhancers such as iodine and AuNPs inside the dosimeter. In gel dosimeter, contrast agents can be impregnated inside the dosimeter itself and therefore the effects of this material can be directly quantified. The tissue equivalent property of polymer gels also serves as a good phantom to simulate the application of medical radiation to the human body. Physical measurement of the dose enhancement produced by high Z materials with other types of radiation dosimeters, such as films and ionization chambers, are quite complicated although there have been some attempts to use these dosimeters[68-69]. The use of dosimeters does have its limits; researchers must rely on Monte Carlo simulation or biological measurement to obtain in vitro or in vivo results. Physical measurements of the dose enhancement produced by high Z materials in normoxic polymer gels have been taken using iodine [70-72]. These studies show that such a contrast agent can be added to nPAG without changing the dose linearity properties of the gel or producing any effects on MRI scanning. The linear relationship between spin-spin relaxation rates and delivered doses is conserved with addition of iodine. Fricke gels have been used to quantify the dose enhancement by gold microspheres before [73]. However, Fricke gels failed to detect the expected increase when used to measure the dose enhancement of iodine, mainly due to their low sensitivity [74] .Also khadem et al achieved 10% absorption dose enhancement with 0.1 mM concentration gold nanoparticle in MAGICA polymer 18 MV energy Linear accelerator [75]. In other research Mahdavi et al studied Effect of Gold Nanoparticle on Percentage Depth Dose Enhancement on Megavoltage Energy in

MAGICA Polymer Gel Dosimeter. Experimental results have shown depth dose increase of 10%, 2% and 4% in 0.1mM, 0.2mM and 0.4mM concentrations, respectively [76]. Ataei et al compare dose enhancement factor of 6MV and 18MV in 0.1mM, concentration gold nanoparticle in MAGICA polymer gel. The results showed that by adding of gold nanoparticles to the MAGICA polymer gel absorbed dose is increased. The levels of polymerization of irradiated gels with and without AuNPs in energy 6MV is more than energy 18MV. It seems that because of the dominance of photoelectric effect at low energies and pair production effect at high energies [77].

Discussion:

3-D dosimetry is a field that has emerged steadily over the last 20 years to a position where there is now a real possibility of useful application in the clinic. Methods of delivery of highly conformed radiation dose currently far outstrip our abilities to measure those same doses routinely in the clinic and it is certain that 3-D methods of measurement will be needed in the future. However, further refinements in technique and improvements in formulation of the dosimeter materials used will continue to be necessary before this method becomes widely accepted.

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