Impact of oxygen on the accuracy and precision of normoxic polymer gel dosimeters

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Abstract. Diffusion of oxygen in normoxic polymer gel dosimeters was studied. Gel samples in glass tubes were exposed to oxygen for different periods and then irradiated. Oxygen inhibited polymerization at the surface and polymerization occurred at larger depths. However the interface between these two regions revealed a local increase of polymerization. $R_2$ values in these distinct regions are analyzed in terms of the concentration of oxygen and of antioxidant. Perhaps counter-intuitively, a small concentration of oxygen increases the sensitivity of the gel by consuming antioxidant molecules. The presence of antioxidant molecules is shown to cause a decrease of sensitivity, presumably through interactions with water free radicals and/or polymer radicals. Mixing and filling procedures as well as oxygen penetration from plastic caps or walls of gel containers are potential sources of oxygen-related discrepancies in normoxic polymer gel dosimeters. This effect may cause dosimetric inaccuracies of up to 60%.

1. Introduction

A comprehensive 3D dose distribution evaluation is crucial requirement for modern 3D radiation therapy treatments. The first three-dimensional dosimetry technique was proposed over a quarter of a century ago when quantitative 3D medical imaging was combined with a novel chemical dosimetry system [1]. It consisted of the well known Fricke solution dispersed in a hydrogel. The utility of this gel dosimeter was limited as the ferric ions generated by ionizing radiation could diffuse rapidly in the gel matrix, distorting the spatial integrity of the measurements. The next generation of gel dosimeters using water soluble monomers was proposed a few years later [2]. The monomers polymerize in chain reactions initiated by the radiation-induced production of water free radicals in the gel. The extent of this chain polymerization is dose-dependent. Unfortunately, oxygen was (and still is) a major concern in the preparation and in the accuracy of polymer gel dosimeters [3]. The reactions between radiation-induced free radicals and oxygen are so effective that polymerization is completely inhibited in polymer gel dosimeters prepared under normal atmospheric conditions. Therefore, these dosimeters must be prepared, cast and sealed under anoxic conditions. It was later proposed that adding a chemical oxygen scavenger (e.g., an antioxidant) to the gel mixture during preparation would yield a radiosensitive gel [4]. These dosimeters were called normoxic, since they could be prepared in normal atmospheric environment.

The salient characteristics of normoxic polymer gel dosimeters have been investigated. Although no dose threshold due to oxygen inhibition is observed in normoxic gel dosimeters, addition of an oxygen scavenger reduces their $R_2$-dose sensitivity compared to their anoxic counterparts.
Discrepancies between the results of different research groups [5] and inaccuracies between the dose delivered to a phantom and the dose determined by normoxic gel dosimeters using calibration vials [6] have been reported. Here we report on the interplay between oxygen and antioxidant molecules within normoxic gel dosimeters. Specifically we demonstrate that oxygen scavengers can also scavenge water free radicals and/or polymer radicals, decreasing the dose sensitivity of normoxic gel dosimeters. Oxygen penetrating the dosimeter by diffusion actually increases the dose sensitivity to some extent, but higher concentration of oxygen eventually decreases the dose sensitivity.

2. Materials and Methods
Diffusion of oxygen was studied in three acrylamide-based and three methacrylic acid-based gel compositions. Tetrakis hydroxymethyl phosphonium chloride (THPC) and ascorbic acid (AscA) were used as antioxidants. Because the initial dissolved oxygen (DO) concentration may depend upon atmospheric conditions, gel fabrication was performed in a nitrogen-filled glove box. The level of oxygen in the glove box was monitored using a Fisher Scientific Accumet® XL60 DO meter. Oxygen level was 0.01 mg/l in the glove box and 0.00 mg/l in nitrogen-bubbled water. Acrylamide-based gels were mixed using concentrations of 5%, 3% and 3% (w/w) of gelatin, acrylamide (AA) and N,N'-methylene-bis-acrylamide (BIS), respectively. Eight glass tubes (KIMAX culture tubes with rubber-lined screw caps, length of 12 cm and volume of 25 ml) were filled. An appropriate volume of THPC was added to half of the remaining solution for a final concentration of 5 mM and a second series of tubes was filled. To the other half, 0.1 mM AscA and 0.02 mM copper(II) sulphate were added. This gives three sets of 8 tubes filled with acrylamide-based gel dosimeters. Methacrylic acid-based dosimeters were prepared from 8% gelatin and 7% methacrylic acid. As above, samples were prepared with 5 mM THPC and 2 mM AscA with 0.08 mM copper(II) sulphate. Three sets of glass tubes were filled and the caps were tightly closed. All the tubes were removed from the glove box and left for 3 h in a fridge for the gels to set. After this delay, caps of the tubes in each set were removed one by one in 12 hours intervals to expose the gels to air. The tubes were irradiated to 5 Gy, 84 h after gel fabrication, with a Gammacell 220 irradiator (Atomic Energy of Canada Ltd.). The machine is equipped with $^{60}$Co sources and had a dose rate of 1.68 Gy/min. Tubes for each type of gel dosimeter were imaged simultaneously 24 h after irradiation with a Siemens Sonata 1.5 T clinical scanner (Siemens Medical Solutions Erlangen, Germany) with a multi-echo spin echo protocol. $R_2$ maps were calculated using in-house software running in MATLAB® environment.

3. Results
Figure 1(A) shows the position of a gel tube and the dose distribution in the Gammacell 220 sample chamber [7]. It is noted that the dose at the bottom and top of the tube is reduced by roughly 5%. Figure 1(B) illustrates spin-spin relaxation rate ($R_2$) values derived from gel tubes containing the acrylamide-based gel dosimeters exposed to air for 24 h. Oxygen diffusion has inhibited polymerization of the PAG dosimeter for the first 33 mm from the surface of the gel. This is seen as a uniform baseline with an $R_2$ value around 1 s$^{-1}$. From this point on, the concentration of oxygen declines to values below the amount required for complete inhibition and $R_2$ rapidly rises to a maximum of 2.4 s$^{-1}$, which is the expected $R_2$-dose response of PAG at 5 Gy. At the bottom of the tube (right of the figure), $R_2$ values decrease by about 4.3% which is consistent with the dose distribution of the Gammacell as shown in figure 1(A). As the time of exposure to air increases the oxygen inhibition front moves deeper into the gel (data not shown).

Less polymer is formed in gels containing antioxidant, which results in lower maximum $R_2$ values along their profiles. Progress of the oxygen inhibition front into the acrylamide-based gels containing THPC (PAGAT) and AscA (PAGIC) is slowed compared to the PAG dosimeter. This is expected due to the presence of antioxidant that reacts with oxygen, preventing it from further diffusion. Interestingly, the behavior of these gels at the oxygen inhibition front is clearly different from that of PAG. Their $R_2$ values rise from the inhibition baseline, reach a maximum and decrease to a relatively steady value roughly 20 mm deeper, presumably after the maximum range of penetration of oxygen.
Percentage differences between maximum $R_2$ values at the top of these maxima and those after the maximum penetration of oxygen is 12.6% for PAGAT and 18.8% for PAGIC.

Figure 1(C) compares oxygen diffusion in an anoxic MAG dosimeter with its two derivatives containing antioxidant. Oxygen has fully inhibited polymerization in the MAG up to 40 mm from the surface of the gel after 24 h. However, for the gels containing antioxidant complete oxygen inhibition was restricted to the first 8 mm from the surface. After the oxygen inhibition front, $R_2$ values of the MAGAT dosimeter sharply increase to a maximum of 19.6 s$^{-1}$ and decrease down to a relatively steady value of 8.7 s$^{-1}$ after a distance of 27 mm from the surface of the gel. The value of the maximum $R_2$ is more than twice of the steady $R_2$ reached after the oxygen diffusion range. In the MAGIC dosimeter, a very sharp peak is observed around 10 mm on the profile followed by a smooth decrease to baseline values. Interestingly, no polymerization is observed after the maximum range of oxygen penetration (30 mm) in this tube. For acrylamide- and methacrylic acid-based gels the features described above were progressively observed deeper into the gel as the duration of exposure to air was increased.

4. Discussion
Reactions of antioxidants have not been specifically studied in polymer gel systems. However, antioxidant activity generally correlates well with radical scavenging activity. It has been shown that oxidation of ascorbic acid proceeds via production of ascorbyl radicals. Ascorbyl radicals react with other free radicals and effectively terminate the propagation of free radical reactions [8]. This is the reason for which AscA is not efficient in acrylamide-based gel dosimeters. We observed no radiation dose response for PAGIC dosimeters containing 0.5 mM of AscA. Interestingly, no polymerization is observed in MAGIC dosimeter after the maximum range of oxygen diffusion into the gel tube. This indicates that the dose sensitivity of MAGIC strongly relies on the presence of oxygen in the solution.

It was suggested that THPC reacts with gelatin in an acrylamide-based dosimeter [5] increasing its coagulation and stiffness and decreasing the $R_2$-dose sensitivity. The coagulation of gelatin is presumed to be uniform in the tubes and we assume that the gelatin network is not affected by the presence of oxygen after the network is formed. Yet, we clearly observe an increase in $R_2$ after the oxygen inhibition front in the gel dosimeters. To explain this observation, we suggest that THPC scavenges radicals during irradiation of the dosimeter, but whether these are water free radicals or polymer radicals, is not known.

![Figure 1](image-url)
Figure 2 shows the $R_2$ profile of the 5 mM THPC PAGAT with the maximum in $R_2$ values after the inhibition baseline highlighted in grey. On the left of this region the concentration of oxygen is high enough to fully inhibit propagation of polymerization and a baseline $R_2$ is measured. The oxygen concentration decreases along the hatched region to presumably zero. It follows that the concentration of THPC molecules (or their normal fragmentation in solution) that have not reacted with oxygen (“unreacted”) is minimal in the first 28 mm of the tube and then increases to a maximum after the maximum range of oxygen penetration. Oxygen and antioxidant strike a balance in the grey region and this results in a larger extent of polymerization. In other words, both unreacted antioxidant and oxygen can lower the extent of polymerization, the absence of these species results in a maximum in the extent of polymerization.

Under ambient atmospheric conditions, the balance between oxygen and antioxidant will depend on the amount of oxygen that penetrates into the solution during stirring, filling and storage of the dosimeter. Any diffusion of oxygen from plastic caps or walls of the containers will further modify the amount of unreacted antioxidant. It should be noted that a variation of 10% on $R_2$ values may translate to a dose discrepancy of up to about 60% when using absolute calibration. As the gel is not unduly exposed to air in conventional gel dosimetry studies, such large discrepancies have seldom been reported. However oxygen-related discrepancies for normoxic gels can lead to poor reproducibility and precision in and between different studies.

5. Conclusion
Normoxic polymer gel dosimeters are not immune to oxygen-related discrepancies. The effect of oxygen may be more visible when using external calibration methods (i.e., when calibration is done with a separate phantom or vials other than the original dosimeter) or when comparing the results of separate gel measurements. Oxygen diffusion through container walls alters the dose response of the gel within a single phantom. This effect may be restricted to the surface or may affect the whole sample, depending on the phantom size and time between preparation and irradiation.
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