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Correlation between ferrous ammonium sulfate concentration, sensitivity and stability of Fricke gel dosimeters exposed to clinical X-ray beams

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ABSTRACT

This work describes the characterization of various *Fricke-Agarose-Xylenol gels* (FXG) dosimeters using NMR relaxometry and MRI analysis. Using X-rays from a clinical linear accelerator (LINAC), the gels were irradiated in the dose range from 0 Gy to 20 Gy. The photon sensitivity of the FXGs was measured in terms of NMR relaxation rates; its dependence on radiation dose was determined as a function of ferrous ammonium sulfate contents (from 0.5 mM to 5 mM). Furthermore, the stability of the NMR signal was monitored over several days after irradiation. These measurements were aided by Magnetic Resonance Imaging (MRI) scans which allowed three-dimensional (3D) dose mapping. In order to maximize the MRI response, a systematic study was performed to optimize acquisition sequences and parameters. In particular, we analyzed the dependence of MRI signal on the repetition time (T_R) and on the inversion time (T_I) using inversion recovery sequences. The results are reported and discussed from the point of view of the dosimeter use in clinical radiotherapy. This work highlights that the optimization of additive content inside gel matrix is fundamental for optimizing photon sensitivity of these detectors.

1. Introduction

The quality assurance of medical procedures that use ionizing radiation is a key element for patient safety and treatment outcome. In particular, the success of radiation therapy in treating cancer depends on the delivery of lethal radiation dose to the tumour, with as little as possible harm to surrounding tissues. The development of accurate procedures for determining radiation dose distributions in three dimensions is of great importance [1–3].

Diamond detectors [4], ionization chamber [5], semiconductor detectors [6], ESR dosimeters [7–29], thermoluminescent dosimeters (TLDs) [23,30–36] and radiochromic film [37,38] can be employed for the dosimetry of photon beams. Diodes and films are valuable for profile measurement and penumbra characterizations [39,40]. However, ionization chambers, diamond detectors, diode, and TLDs are not suitable for the rapid and quantitative mapping of radiation distributions over the target volume and are not able to resolve high dose gradients. Radiochromic films map 2D dose distributions, from which 3D dose distributions may be reconstructed. Alanine ESR dosimeters offer favorable features such as tissue equivalence, linear response and high stability, but their minimum detectable dose is quite high, around 1 Gy.

In 1984, Gore et al. [41] suggested that aqueous gels containing a ferrous sulphate solution [42–44] could be employed in

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conjunction with Magnetic Resonance Imaging (MRI) to determine radiation dose distributions. MRI is inherently a three-dimensional method and is well known for its ability to provide structural information in a variety of samples. The Fricke gel system, extensively studied in literature [45–51], is based on the radiation-induced oxidation of Fe^{2+} into Fe^{3+} and this process is dose-dependent [52,53].

The oxidation of ferrous ions also brings about a reduction of the longitudinal nuclear magnetic relaxation time T_1 [54] which can be measured by means of nuclear magnetic resonance (NMR) relaxometry and Magnetic Resonance Imaging (MRI). A T_1–weighted MRI sequence is able to discriminate between regions with different absorbed dose [46,55]. The crucial goal is the use of MRI to determine three-dimensional dose distribution [56]. Different type of gels have been used as tissue-equivalent media [57,58]. The most common matrices investigated were porcine gelatin [54,59,60], agarose [61], Sephadex [52] and polyacrylamide [62]. Each of these systems had its advantages and limitations, but agarose is probably the most common gelling agent used for gel detectors. However, there is one major drawback related to this gel medium, that is the ferric ions produced in the irradiated gel region are able to diffuse throughout the dosimeter.

In this paper, we present the results obtained by measurements of NMR relaxometry and MRI of Fricke-Xylenol gels made using agarose as gelling agent. The samples were exposed to radiotherapy-level doses of high-energy X-rays from a linear accelerator (LINAC). Several different gel compositions were investigated with different ferrous contents in the gel matrix, aiming at optimizing the samples response and at evaluating the signal stability over several days after irradiation. In particular, we analyzed how the relaxation rates R_1 $(1/T_1)$ are affected by irradiation. We also evaluated the MRI signal for possible application in 3D photon beam dosimetry and performed a systematic study to optimize acquisition sequences and parameters for MRI response maximization. In particular, we analyzed the dependence of MRI signal on the repetition time T_R and on the inversion time T_I using inversion recovery sequences.

2. Materials and methods

2.1. FXGs preparation

Fricke gel solutions were prepared using agarose at 3% (Sigma–Aldrich®), in H_2SO_4 25 mM obtained adding Suprapure H_2SO_4 (96%) (Merck®), variable concentrations (from 0.5 mM to 5 mM) of ferrous ammonium sulphate hexahydrate (Mohr salt $[Fe(NH_4)_2(SO_4)_2{*}6H_2O]$ (Sigma–Aldrich®) and 0.165 mM of xylenol orange-sodium salt $C_{31}H_{28}O_{13}N_2Na_4$ (Sigma–Aldrich®), which is ferric ion indicator. Gels were prepared following a slight modified version of the procedure described in [59]. In particular, agarose dissolution in hot water (50% of the total water) was performed by using a CEM STAR System 2 *(CEM Corporation, Matthews, North Carolina)* microwave open cavity digestor, setting the following temperature parameters: 2 min at 90 °C (step 1). During this step the agarose is added to water. Then, the system was set at the boiling point for 20 min (step 2) to completely dissolve the agarose. A glass rod was used to mix thoroughly the chemicals. *Ultrapure Water (UPW)* (resistivity 18.6 MΩ ∗ cm) was used for preparation. And a condenser was used to avoid any losses of vapor. When the agarose solution had reached a temperature of 70 °C, the Fricke solution (made with the remaining 50% of water, sulfuric acid, ferrous ammonium sulphate and xylenol orange sodium-salt) was added to the agarose and mixing was aided by gentle stirring. When the solution reached 50 °C, it was poured in acrylic molds and conditioned for the formation of gel and its subsequent irradiation. The FXG dosimeters were maintained under refrigeration (10 ± 1 °C) and in a dark environment after the preparation and between irradiation and measurement in order to minimize the self-oxidation of the iron presents in the gels due to temperature and light.

2.2. Irradiation

The gels were exposed to absorbed doses between 0 and 20 Gy of 6 MV X-rays at the radiotherapy department "U.O.C.-Fisica Sanitaria A.R.N.A.S. Ospedale Civico" in Palermo, Italy. A build-up layer was placed on the samples and all photon irradiations were done under electronic equilibrium conditions. This set-up is routinely used for treatment of patients. The photon absolute dose values were measured using an ionization chamber.

2.3. Instrumentation

NMR relaxometry measurements were performed using an mq-ProFiler single-side relaxometer (Bruker Biospin®, Italy) operating at a frequency of about 15 MHz. Longitudinal relaxation times were acquired by saturation-recovery spin-echo sequences. In this case, we obtained relaxation trendlines of the NMR signal as function of the saturation time (T_S), which is the time between the first and the second 90°-pulses. These trendlines are related to the recovery of the longitudinal magnetization after a first 90° pulse; they start from zero and tend to saturate to a maximum value. The acquisition was carried out for various values of recovery delay T_S, ranging from 0.1 ms and 8500 ms. The interpulse delay for spin-echo signals was 44 μs, *i.e.* the shortest possible delay. After each sequence, a recycle delay of 1.2 s was set to allow the longitudinal magnetization to fully recover before next pulse sequence. Each measurement was the average of 16 subsequent accumulations. All measurements were carried out at room temperature, carefully keeping the samples away from light. MRI imaging was done on a 1.5 T *Achieva scanner (Philips®, Best, the Netherlands)* with an eight channel head coil, using the Inversion Recovery Sequence (optimized for brain). The T_1–weighted MRI images were calculated from the individual MR images using Philips software. In order to evaluate the dependence of the MRI signal from the parameters of the sequence, the acquisitions have been made by setting different T_R and T_I. The specific imaging parameters are shown in Table 1. All measurements were performed at room temperature. The samples were scanned about four hours after the irradiation. The samples were maintained at least 30 min at room temperature before the MRI evaluations. The intensity of the signal was calculated with the MIPAV software tools (*Medical Image Processing, Analysis and Visualization*) version 7.0.1. (http://mipav.cit.nih.gov/).

3. Results and discussion

3.1. NMR measurements

Analyses were carried out on the behavior as function of dose of the longitudinal and transverse nuclear relaxation of different FXG

Table 1
MRI image acquisition parameters.

T_E (ms)	18
T_I (ms)	from 300 to 2000
T_R (ms)	from 500 to 3000
N° acquisitions	1
Voxel dimension	$0.37 \times 0.37 \times 6.00$ mm^3
Matrix size	640×640 pixel^2