IL NUOVO CIMENTO **43 C** (2020) 147
DOI 10.1393/ncc/i2020-20147-7

COLLOQUIA: SIRR 2020

Practical role of polymerization inhibitors in polymer gel dosimeters

G. MAGUGLIANI(1), G. M. LIOSI(1), M. MARRANCONI(2), E. MICOTTI(3), M. CAPRIOLI(1), A. GAMBIRASIO(2), F. LOCATELLI(2), E. MACERATA(1), E. MOSSINI(1), P. SALMOIRAGHI(2), L. TROMBETTA(2), V. VAVASSORI(2), G. FORLONI(3), M. MARIANI(1) and E. BOMBARDIERI(2)

(1) *Department of Energy, Nuclear Engineering Division, Politecnico di Milano Milano, Italy*
(2) *Cliniche Humanitas Gavazzeni - Bergamo, Italy*
(3) *Laboratory of Biology of Neurodegenerative Disorders, Department of Neuroscience, Istituto di Ricerche Farmacologiche Mario Negri IRCCS - Milano, Italy*

received 25 January 2021

Summary. — The fundamental role of pre-treatment quality assurance in radiotherapy is to verify the radiation treatment with respect to the planned dose distribution by means of a devoted dosimeter. This step is necessary to achieve the full clinical potential of the treatment by guaranteeing sparing of healthy tissues. In this study, the dose response of a modified version of the PAGAT polymer gel dosimeter, a chemical dosimeter capable of direct 3D dose measurements, has been characterized. The physical response of the dosimeter is proportional to polymerization efficiency between its constituting monomers. The effect of several polymerization inhibitors in controlling the chemical response of the gel was investigated. The addition of these compounds allows a tailoring of the range of dose response of the gel to the dose range used in clinical practice. Obtained results from optical and magnetic resonance imaging analyses of irradiated gels indicate that an accurate control of inhibitor concentration can lead to a significant extension of the useful dose range, from approximately 4 Gy for the reference composition up to 40 Gy when inhibitors are added, with no significant detriment on fundamental dosimetric parameters such as accuracy, dose resolution and stability of the dose response.

1. – Introduction

In order to achieve optimal and ever-improving clinical outcomes, modern radiotherapy (RT) strongly relies on spatial conformity of delivered dose to the geometry of the lesion to be treated. The underlying rationale is that reduction in the exposure of healthy tissues in proximity of the treatment volume spares them from the short- and long-term side effects induced by radiation, therefore resulting in the potential increasing of the

therapeutic window of the treatment. In order to fully exploit the technical capabilities of modern linacs in volumetric modulation of radiation fluence, treatment sessions are planned and optimized via the use of dedicated simulation software, *i.e.*, treatment planning systems (TPS) [1]. Verifying the compliance between simulated and delivered dose distributions is the goal of patient-specific Quality Assurance (QA). From a metrological point of view, QA of volumetric treatments requires a dosimetric system with high spatial precision and accuracy. An ideal dosimeter dedicated for this task should also feature an intrinsic 3D probing capability.

Research in the field of polymer gel dosimetry is motivated by the current lack of a universally recognized golden standard for direct three-dimensional pre-treatment dosimetry [2], a paramount task in the overall process of patient QA. Polymer gel dosimeters are under research thanks to their intrinsic three-dimensional dose response [3], coupled with tissue equivalent composition [4] and good sensitivity in the dose range employed in RT.

Physical response of polymer gels derives from radiation-initiated free radical polymerization between monomers, resulting in the formation of sub-micrometric polymeric particles [5] which remain suspended and localized in a gelatinous matrix. Their spatial concentration is thus directly related to the three-dimensional dose deposition geometry. The concentration and size of these polymeric domains represents the physical response of the dosimeter. Radiation-initiated polymerization induces alterations of optical and nuclear magnetic resonance properties of the gels, that can be probed through UV-Vis spectrophotometry and R_2-weighed magnetic resonance imaging (MRI) [3]. These techniques are endowed with different advantages and weaknesses, due to specific physical phenomena which they probe, *i.e.*, light scattering by polymer particles and accelerated spin-spin relaxation rate due to higher concentration of rigid polymeric structures, respectively, for optical and MRI techniques.

In the RT pre-treatment dose validation processes, polymer gels are typically used in a relative manner to acquire a relative map of the 3D dose distribution by rescaling treatments to cover the range of response of the dosimeter [6]. Since delivered doses in RT can typically range from 2 Gy up to and beyond 25 Gy per fraction, an ideal passive dosimeter should respond linearly in the same dose range. Adapting the planned treatment dose to the range of linear response of the dosimeter through a down- or up-scaling, could in fact be detrimental. Large rescaling of the treatment dose, while maintaining the same linac dose rate prescription, can potentially challenge the mechanical performance of the linac components in the beam-delivering process, possibly introducing additional undesired uncertainties [7]. On the other hand, a too large range of linear response compared to the treatment maximum dose, involves an undesirable loss in dosimeter sensitivity. The range of response of a chemical dosimeter is in fact inversely proportional to its sensitivity, and therefore the highest sensitivity and dose resolution will be both achieved by setting the dose response as close as possible to the individual treatment maximum dose.

In polymer gel dosimeters saturation of response and loss of linearity are a consequence of the depletion of available monomers in the solution as the absorbed dose increases [8]. The useful dose range is therefore influenced by the efficiency of polymerization and could be controlled by altering the kinetics of the process. In this study, the effect of polymerization inhibitors on the overall dose response of the polymer gel PAGAT was investigated. This polymer gel dosimeter, as characterized in the following sections, presents a response limited to roughly 4 Gy. This dose range is therefore not adequate for direct coverage of the whole dose range of interest in RT. As mentioned previously, the response of polymer gels derives from free radical polymerization, a process defined as

"chain polymerization in which the kinetic-chain carriers are radicals" [9]. Chain growth proceeds through interaction between radical-bearing extremities of polymer chains and monomers. The three main steps involved in radical polymerization are initiation, propagation and termination [10]. In polymer gel dosimeters, initiator species are formed by the interaction of radiation with matter, leading to the production of reactive compounds that can further propagate polymerization via the addition of monomers [3]. Relative kinetics of initiation, propagation and termination regulate the polymer yield, *i.e.*, the physical response of the dosimeter and its range of response. In industrial applications of radical polymerization, specific compounds can be used with the goal of regulating the chemical behavior and stability of monomeric solutions undergoing polymerization. A class of these compounds, known as *inhibitors*([1]), can be employed to control the kinetics of radical polymerization. In general, these act as scavengers by exhibiting high affinity to propagating or initiator radicals. Inhibitors are typically employed to increase shelf life of stored monomers by preventing premature polymerization, or to modify polymeric properties through control of reaction kinetics [10].

This study had the goal of characterizing whether polymerization inhibitors could be employed in polymer gel dosimeters to quantitatively regulate their range of response and sensitivity, without detrimental effects on fundamental dosimetric quantities such as dose resolution, precision and chemical stability. To this goal, compounds of relevance in the polymer industry have been identified, and their effect on the dose response of the polymer gel PAGAT has been investigated.

2. – Materials and methods

2˙1. *Dosimeter preparation.* – The formulation of the PAGAT dosimeter employed in this study was as follows (weight percentages): 89% deionized water, 5% gelatin (gel strength 300, type A, from porcine skin), 3% acrylamide (AA), 3% N,N′-methylenebisacrylamide (BIS), 10 mM Tetrakis(hydroxymethyl)phosphonium chloride (THPC). This basic formulation will be indicated as *reference composition*. This has been modified by adding different inhibitors in varying concentrations. For this preliminary investigation, each inhibitor was tested individually since, in general, the simplest composition yielding the required performance should be sought in order to limit the number of variables to be controlled during preparation. Tested inhibitors, with their respective investigated concentration range, are reported in table I. These compounds have been selected in order to, ideally, present good efficacy at low concentration, not to worsen the tissue equivalence of the reference composition or pose additional problems of induced toxicity. Throughout this work, parts per million/trillion notations (ppm/ppt) indicate weight fractions.

Dosimeters were manufactured according to a procedure standardized to be reproducible and easily scalable. Dosimeter preparation is carried out as follows. The required amount of water is divided in two equal portions. In one fraction, AA and BIS are dissolved by stirring at 50 °C for 30 minutes. In the meantime, gelatin is dissolved in

([1]) In the field of polymer chemistry, a distinction is often made between *inhibitors* and *retarders*: the former are considered to act on initiator derived radicals, while the latter on propagating radicals, with therefore different effects on the overall polymerization kinetics. However, IUPAC considers both terms as synonyms, so no distinction in terminology is made throughout this work.

TABLE I. – *Investigated polymerization inhibitors and respective concentration range. Each inhibitor was tested individually.*

Inhibitor	Concentration range (ppm)
$CuCl_3$	10–100
Nitrobenzene	0.001–100
Hydroquinone	10–5000
p-nitrophenol	0.1–10

the remaining water fraction at 50 °C. Once both solutions are uniform and particulate is no more visible, they are allowed to cool naturally below 30 °C. Temperature control during dissolution and final mixing is important, in order to prevent premature heat-induced polymerization [11]. Once both solutions have cooled, they are combined under gentle stirring, avoiding incorporation of air. At this point, the appropriate inhibitor is added, followed by THPC. Scavenging of dissolved oxygen by THPC is completed within few minutes [12], and the dosimetric solution must be poured and sealed in the appropriate container within this time frame. For this study, the dosimetric solution was transferred in spectrophotometric cuvettes (PMMA, $5 \times 1 \times 1$ cm), which were stored under refrigeration at 3 °C for at least 12 h before use.

2˙2. *Irradiation.* – Irradiations were performed with a Varian Trilogy linac (Varian Medical Systems, Inc). X-ray beam settings were 6 MV nominal energy, 600 MU/min nominal dose-rate. The geometry of the beams involved gantry positions at 0 ° and 180 °, with beam rectangular shape of 200 mm along the cross-line direction and 300 mm along the in-line direction. Delivered doses extended up to 40 Gy for the most inhibited compositions. Cuvette samples were positioned in a tissue equivalent RW3 slab phantom (PTW Freiburg GmbH), longitudinally with respect to the gantry axis. The geometric center of the cuvettes, taken as their reference point, was positioned at the isocenter of the treatment fields. This positioning, combined with posterior/anterior and anterior/posterior irradiation, allowed to achieve a dose uniformity ∼99% over the sensitive volume of the samples as planned by TPS. Prior to irradiation, cuvette samples were allowed to thermalize to room temperature. At least four samples from each composition were considered for each tested dose, in order to allow statistical evaluations on intra-batch uniformity and precision. After irradiation, samples were stored at 3 °C for at least 12 h to allow development of chemical response.

2˙3. *Optical and MRI analysis.* – Evaluation of physical response of the dosimeters was performed both via UV-Vis optical and MRI measurements.

UV-Vis optical analyses were performed with a LAMBDA 650 UV-Vis spectrophotometer (PerkinElmer Inc.). Absorbance values for each sample were measured against a deionized water reference. Net absorbance values ΔAbs_i for each irradiated sample i were calculated as

$$\Delta Abs_i = Abs_i - \overline{Abs}_b,$$

where $\overline{Abs}_b$ is the average absorbance of blank samples and Abs_i is the uncorrected absorbance of sample i.

To perform MRI measurements, a Philips Achieva 1.5 T scanner equipped with head/neck SENSE/NV 8 channel coil (Philips N.V.) was employed. For analyses, cuvette

samples were grouped and immersed in a water bath at 23 °C, for the purpose of a) providing thermal inertia to the samples to avoid undesired temperature increase during scanning and b) limit susceptibility artifacts which could interfere with the acquired images in the proximity of air/cuvette interfaces. Acquisitions were performed with a gradient spin echo (GraSE) pulse sequence (echo time 40 ms, 14 echoes, repetition time 4000 ms). A typical high-resolution 1 mm isotropic voxel acquisition of a cuvette group comprising 10 transverse slices (square FOV, 190 phase encoding steps, number of signal averages = 6) required roughly 30 minutes. Raw data from MRI acquisitions was processed in order to extract R_2 values on a pixel-by-pixel basis from signals at increasing echo time by interpolation against appropriate Block equation. A chi-squared minimization algorithm implemented in the MATLAB environment (The MathWorks, Inc.) has been adopted for this scope [6]. After reconstruction of a R_2-weighed image, mean R_2 values for each cuvette sample were determined by ROI averaging over the transverse section of the sensitive volume of the gel. Similarly as for UV-Vis analyses, also for MRI data net relaxation rate for sample i was determined as

$$\Delta R_{2,i} = R_{2,i} - \bar{R}_{2,b},$$

where $\bar{R}_{2,b}$ is the average transverse relaxation rate of blank samples and $R_{2,i}$ is the uncorrected relaxation value of sample i.

The sensitivity S of each dosimetric composition was defined as the slope of the linear fit in a dose-response plot. Even if the dose response of polymer gel dosimeters is intrinsically best described by a bi-exponential fitting function [13], as also illustrated experimentally in the following section, the adopted definition of sensitivity based on linearity is still useful to draw quantitative comparisons between different formulations. Dose resolution, *i.e.*, minimum difference in dose that can be measured with 95% confidence, is calculated as reported in literature [6]:

$$Dose\ res = 2.77\frac{\bar{\sigma}}{S},$$

where $\bar{\sigma}$ is the average standard deviation of samples laying in the range of linear response. In reported graphs throughout this work, error bars represent one standard deviation of uncertainty.

2˙4. *Results*. –

2˙4.1. PAGAT —reference composition. Dose response of the reference composition of the PAGAT gel is reported in fig. 1 and table II. The gel expresses good linearity to low doses (∼3 Gy), precision and reproducibility. Post-irradiation stability is achieved 24 h after irradiation, after which the dosimetric performance remains stable for at least one week afterwards. Above the linearity threshold of 3 Gy, the response of the gel starts to depart from linearity, and it is best described by a bi-exponential fitting function. Nonetheless, above 4 Gy response saturation becomes severe, resulting in very poor resolution due to very low sensitivity.

2˙4.2. $CuCl_3$. $CuCl_3$ does not show any inhibition effect in the tested concentration range (10–100 ppm). It may be possible that higher concentrations could improve the inhibition efficiency. However, increasing the concentration of high-Z elements such as copper in the dosimeter could worsen its tissue equivalence characteristics, especially at

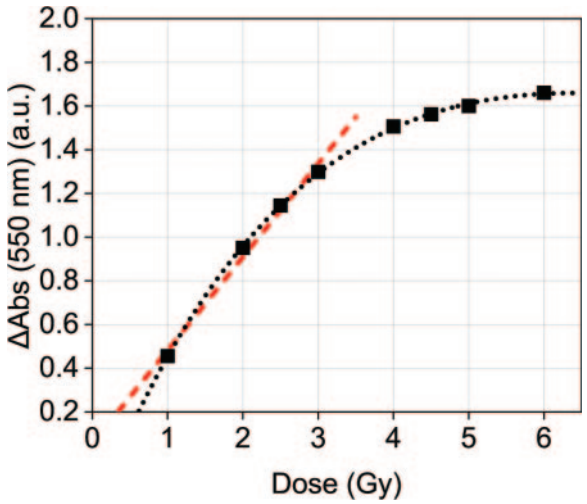

Fig. 1. – Optical dose response of the reference PAGAT gel expressing good linearity up to 3 Gy ($R^2 = 0.989$). Analysis performed 24 h after irradiation.

lower photon energies. This factor discouraged further investigations with this compound in favor of the other inhibitors.

2˙4.3. Nitrobenzene. Nitrobenzene presents very efficient inhibition. At concentrations greater than 1 ppm the dosimeter expresses an extremely faint, but measurable, response, roughly two orders of magnitude lower than that of the reference composition, extending beyond 20 Gy. This behavior is indicative of very efficient inhibition on polymerization propagation. The very faint response is likely due to low-molecular-weight polymeric particles that managed to form before the inhibitor could interact with polymer radical ends. This behavior suggests that under these conditions nitrobenzene primarily acts on propagating radicals [10]. As a reference, samples irradiated at 2 Gy presented an

TABLE II. – *Summary of dosimetric performance of different compositions of the PAGAT gel. Reported values have been measured via UV-Vis optical analysis: 550 nm at 24 h post-irradiation (reference composition, p-nitrophenol) and at 72 h post-irradiation (hydroquinone, nitrobenzene).*

	Inhibitor (concentration)			
	None-reference composition	Hydroquinone (5000 ppm)	Nitrobenzene (1 ppb)	p-nitrophenol (7.5 ppm)
Dose range [Gy]	4	12	12	>40 Gy
Sensitivity [Gy^{-1}]	0.43 ± 0.01	0.13	0.121 ± 0.003	0.0148 ± 0.0001
Dose resolution [Gy]	0.12	0.50	0.83	0.86
Average precision	1.2%	1.6%	>10% below 6 Gy <3% above 6 Gy	3.2%

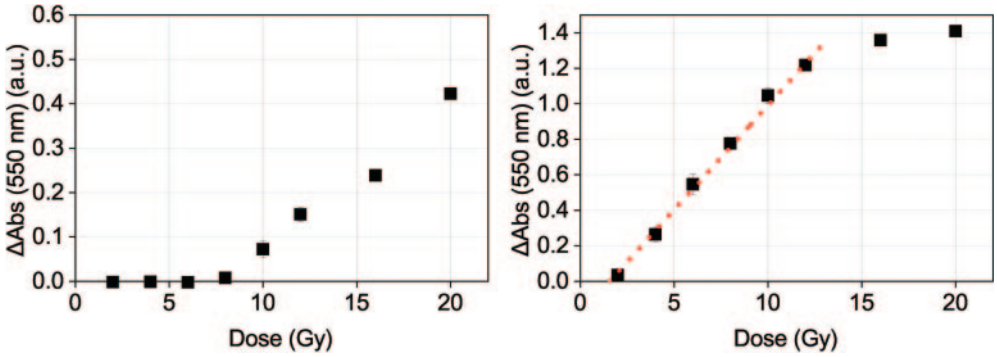

Fig. 2. – Optical response of PAGAT: 100 ppb nitrobenzene (left) and 1 ppb nitrobenzene (right). Analysis performed 72 h after irradiation. A marked dose threshold is visible for the 100 ppb composition, extending up to 8 Gy, after which the dose response regains linearity. Also in the case of the 1 ppb composition, a small dose threshold is indicated by the non-zero intercept of the otherwise excellent linear fit ($R^2 = 0.996$).

average ΔAbs of 0.031 ± 0.005 (100 ppm): precision at these nitrobenzene concentrations is therefore very poor. Also this factor is likely due to low polymerization yield, resulting in very high dispersity and therefore in optical properties of the gel.

Due to the above-mentioned limitations outlined by PAGAT formulation with 1 ppm nitrobenzene, it was decided to reduce the concentration of the inhibitor. The formulation at 100 ppb concentration presents a much more intense response, but also a very pronounced dose threshold effect extending up to 8 Gy (see fig. 2, left). The presence of a dose threshold effect is a characteristic consequence of the presence of strong polymerization inhibitor in the dosimetric solution: once the upper limit of the threshold has been reached, the inhibitor has been consumed. This behavior can also be observed in the case on incomplete oxygen scavenging [11]. From a dosimetric point of view, such a high threshold is obviously not acceptable. By further lowering inhibitor concentration to 1 ppb, this threshold is reduced but is nonetheless present (see fig. 2, right). This is indicated by the fact that the intercept of the linear interpolation does not pass from zero. In order to further reduce this effect, an even lower inhibitor concentration would be needed. However, already for concentrations of 1 ppb (*i.e.*, nanomolar), problems of reproducibility and precision start to become significant due to intrinsic difficulties in guaranteeing chemical uniformity, both intra- and inter-batch, at such low concentrations. This factor is underlined by the very poor precision of this composition (see table II). The fact that average precision tends to improve with the increase of absorbed dose hints at some non-homogeneity in inhibitor concentration between samples: as the irradiation progresses and nitrobenzene is consumed, samples regain uniformity in their behavior. An additional drawback of formulations containing nitrobenzene consists in the long time required to achieve full response development, which amounted to at least 72 h after irradiation.

2˙4.4. Hydroquinone. Hydroquinone has already been proposed in literature as a polymerization inhibitor in polymer gel dosimeters, but with a different role than that explored in this paper: when added in very low concentrations, it has been shown to inhibit spontaneous polymerization in blank samples and increase the available R_2 range under MRI analysis [14, 15]. The effect on irradiated samples at those concentrations is how-

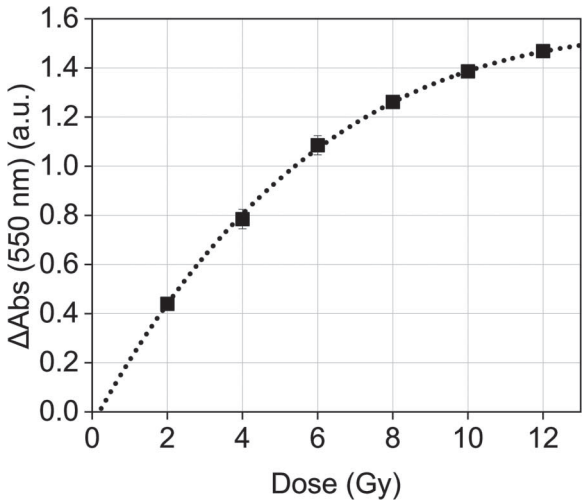

Fig. 3. – Optical response of PAGAT: 5000 ppm hydroquinone. Analysis performed 72 h after irradiation.

ever negligible, and no extension of the range of linear dose response can be observed. In this study, much greater concentrations of hydroquinone have been tested. In these conditions, the effect on blank samples is obviously preserved, but inhibition effects start to become appreciable also on irradiated samples.

The effect of hydroquinone is quantitative and proportional to its concentration. The lowest concentration that results in measurable effects on the dose range of the gel is 100 ppm. Lower concentrations do not show effects on the response of irradiated samples, but nonetheless contribute to limit spontaneous polymerization in blank samples. Dosimeters prepared with 5000 ppm hydroquinone show remarkable, and reproducible, extension of the dose range up to 12 Gy (see fig. 3). Contrarily to the case of nitrobenzene, for this composition no dose threshold is apparent. On the downside, the dose response reaches stability only 72 h after irradiation, and it can be effectively described only via bi-exponential behavior. Concentrations higher than 5000 ppm have not been tested, due to the approaching of the solubility limit of the compound and related difficulties in guaranteeing complete and reproducible dissolution in the limited time interval of dosimeter preparation.

2˙4.5. p-nitrophenol. p-nitrophenol presents far superior behavior to all other inhibitors tested. Depending on its concentration, the range of dose response can be extended beyond 40 Gy, preserving excellent linearity and dosimetric performance (see table II). A marked inhibition effect can be achieved with low concentrations in the ppm range. Working in this concentration range is ideal, since it avoids the inconveniences encountered with nitrobenzene (difficulty in guaranteeing reproducibility in the lower ppb range) and with hydroquinone (practical solubility limit) mentioned in the previous paragraphs.

Composition containing 7.5 ppm nitrophenol presents an ideal compromise between inhibition and sensitivity. Its dosimetric performance is reported in table II. This composition expresses excellent linearity ($R^2 = 0.996$) up to 40 Gy under optical analysis (see fig. 4, left). The excellent dosimetric response of this composition has been verified also

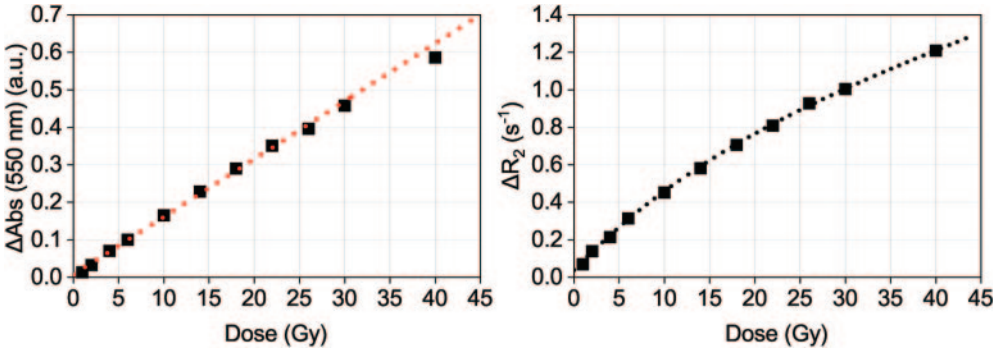

Fig. 4. – PAGAT: 7.5 ppm p-nitrophenol. Optical analysis (left) and MRI analysis (right). Both analyses were performed 24 h post-irradiation.

via MRI analysis, which confirmed the absence of significant signs of saturation up to the maximum tested dose (see fig. 4, right). In this case, the response is best described by the aforementioned bi-exponential fit [3]. Under both analytical techniques, the dosimetric response appears as fully developed within 24 h post-irradiation, as is the case for the reference PAGAT composition. This is a desirable characteristic which allows for faster dosimetric evaluations after delivery and improves clinical usability of the gel system.

3. – Conclusion

Several polymerization inhibitors ($CuCl_3$, nitrobenzene, hydroquinone and p-nitrophenol) have been tested, with the aim of increasing the useful dose range of the reference literature composition of the polymer gel dosimeter PAGAT.

The effect of such compounds was investigated at different concentrations, in order to establish which composition could yield optimal results in terms of dosimetric precision, sensitivity, resolution and reproducibility. Addition of inhibitors results in significant lowering of spontaneous polymerization in blank samples, thus increasing the pre-irradiation stability of the gel. The addition of these compounds does not result in the superposition of additional optical absorption peaks in the visible spectrum. Moreover, since they (with the exception of $CuCl_3$ which anyhow did not achieve measurable effects) are constituted by CHON elements, their addition does not introduce susceptibility effects during MRI scanning. These factors are very favorable for easier and more reproducible optical and MRI analyses.

Nitrobenzene and hydroquinone achieve measurable effects on the dose range of the polymer gel, allowing a quantitative control of its response. However, they both express some practical limitations: the former, requiring an optimal concentration in the low-ppb range, presents difficulties in achieving chemical uniformity. The latter, on the contrary, requires very high concentrations that approach the solubility limit of the compound, posing technical difficulties during dosimeter preparation. Due to these factors, the dosimetric performance deriving from the use of these compounds does not comply with the criteria required for clinical dosimetry.

The addition of p-nitrophenol, on the other hand, results in very promising dosimetric performance, both under MRI and UV-Vis optical analysis. This inhibitor is able to quantitatively regulate the dose response of the gel, by extending it even above the dose

range of current clinical significance, *i.e.*, roughly 25 Gy, with no detrimental effects on other dosimetric parameters such as precision and dose resolution.

Due to overall superior performance of the p-nitrophenol PAGAT composition, further characterization activities will be focused on this formulation. As is known, several irradiation parameters such as duration and fractionation can induce undesired uncertainties in the response of polymer gels [16, 17]. The influence of these factors on the response of the gel will need to be characterized in order to determine whether such modified version of the PAGAT dosimeter could be effectively employed in RT dosimetry.

* * *

This study was supported by Fondazione Humanitas per la Ricerca with funding from Italian 5×1000 donations, and H2020-Euratom-1 project A-CINCH (Grant agreement ID: 945301).

REFERENCES

[1] Ezzell G. A. *et al.*, *Med. Phys.*, **30** (2003) 2089.
[2] Podgorsak E. B., *External photon beams: physical aspects*, in *Radiation Oncology Physics: A Handbook for Teachers and Students* (International Atomic Energy Agency, Vienna) 2006, Chapt. 6.
[3] Baldock C. *et al.*, *Phys. Med. Biol.*, **55** (2010) R1.
[4] Un A., *Appl. Radiat. Isot.*, **2** (2013) 258.
[5] Oldham M. *et al.*, *Med. Phys.*, **30** (2003) 623.
[6] De Deene Y. *et al.*, *Phys. Med. Biol.*, **47** (2002) 3117.
[7] Park J. M. *et al.*, *Br. J. Radiol.*, **88** (2015) 20140698.
[8] Schreiner L. J. *et al.*, *J. Phys.: Conf. Ser.*, **250** (2010) 012014.
[9] International Union of Pure and Applied Chemistry, *Compendium of Chemical Terminology*, 2nd edition (Blackwell Scientific Publications, Oxford) 1997.
[10] Moad G. *et al.*, *The Chemistry of Radical Polymerization*, 2nd edition (Elsevier) 2005.
[11] De Deene Y. *et al.*, *Phys. Med. Biol.*, **45** (2000) 859.
[12] Jirasek A. *et al.*, *Phys. Med. Biol.*, **51** (2006) 1891.
[13] De Deene Y. *et al.*, *Phys. Med. Biol.*, **51** (2006) 653.
[14] Venning A. J. *et al.*, *Phys. Med. Biol.*, **50** (2005) 3875.
[15] Hurley C. *et al.*, *Appl. Radiat. Isot.*, **63** (2005) 443.
[16] Magugliani G. *et al.*, *Radiat. Eff. Defects Solids*, **173** (2018) 784.
[17] Karlsson A. *et al.*, *Phys. Med. Biol.*, **52** (2007) 4697.