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FERROUS-SULPHATE-DOPED AGAROSE GELS FOR N.M.R. DOSIMETRY. 3-DOSE DETERMINATIONS IN B.N.C.T. AND DEPTH-DOSE PROFILING IN PROTON THERAPY

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ABSTRACT

In recent radiotherapy techniques, such as Boron Neutron Capture Therapy (BNCT) and proton-therapy, the high non-uniformity of the spatial distribution of absorbed dose requires 3-D dose determinations, in order to perform good planning of treatments. The aim of this work is the setting up of a phantom-dosimeter which allows three-dimensional measurements of absorbed dose. The phantom is composed of a chemical dosimeter (ferrous sulphate solution) incorporated in a gel (Agarose). Ionising radiation causes a variation in the relaxation rates of hydrogen nuclei, measurable by Nuclear Magnetic Resonance (NMR) analysis. The spatial distribution of absorbed dose can therefore be determined through an NMR imaging of the phantom-dosimeter after irradiation.

1. - INTRODUCTION

The present objective of radiotherapy is the achievement of a relevant energy deposition in tumours, with low energy release to surrounding healthy tissue.

An interesting and promising approach to the question is that chosen by Boron Neutron Capture Therapy (BNCT), which takes advantage of the possibility of accumulating boron nuclei in cancerous tissue, and of the high cross section ($\approx$ 3840 barns) of the isotope ^{10}B for the reaction with thermal neutrons $^{10}B(n,\alpha)^{7}Li$. The short range of the emitted α and ^{7}Li particles allows localised energy deposition. A selective destruction of cancerous tissue is therefore achieved if a high ratio between boron concentration in the tumour and that in surrounding tissue is attained. To test the validity of the therapy and to carry out the planning of the treatment, exhaustive information on the spatial distribution of absorbed dose is desirable. We have undertaken the study and the setting up of a system which allows three-dimensional determinations of absorbed dose. The system is composed of a chemical dosimeter incorporated into a tissue-equivalent gel with which it is possible to compose phantoms simulating the situations of interest. The phantoms act as dosimeters at the same time; in fact, after exposure they may be conveniently examined with NMR analysers, and thus the spatial distribution of absorbed dose is detectable. The results obtained so far are promising, and have encouraged further investigations aimed at inquiring into the applicability of the dosimeter to other radiotherapy modalities.

Among the new radiotherapy techniques aimed at obtaining a high absorbed dose in tumours with low dose delivered into surrounding tissue, a fundamental role is played by proton therapy, which is at present in the course of development and improvement. In fact, charged particles, and in particular protons, in a medium release a high dose at the end of their range, that is at a depth which is a function of both the energy of particles and the composition of the medium itself. It is therefore an obvious requirement, for treatment planning to get depth-dose profiles with good spatial resolution. Many experimental and theoretical methods for depth-dose profiling are currently developed and employed. We hope to give a useful contribution to this important topic. We have carried out a feasibility test of dose profiling by means of a system composed of the chemical dosimeter incorporated into tissue-equivalent gel. The encouraging results, revealing auspicious and profitable characteristics of the dosimeter, have stimulated the continuation of the research in order to set up the system and to improve the possibility of employment.

2. - THE DOSIMETER

The proposed system is composed of a chemical dosimeter incorporated into a gel. The chosen gelling agent, whose role is that of maintaining the spatial localisation of absorbed dose, is the polysaccharide Agarose SeaPlaque (from Fluka Chemical Corporation), because this gel has brought the best results as regards both dosimeter sensitivity and result reproducibility. The chemical dosimeter is a ferrous sulphate solution, which is the main constituent of the standard Fricke dosimeter. In such a solution ionizing radiation produces a conversion of ferrous ions (Fe^{2+}) to ferric ions (Fe^{3+}). In a certain dose interval the ferric ion concentration has been shown to be linearly correlated to the absorbed dose[1]. The ferric ion yield is dependent on the dosimeter composition. For a ferrous sulphate solution incorporated into a gelatine the G value (i.e. Fe^{2+} oxidised per 100 eV absorbed energy) is higher than that of the standard Fricke dosimeter.

A thorough experimental study has been made to optimise the preparation protocol and the composition of the dosimeter, in order to achieve good sensitivity and good result reproducibility. The requirements for different applications of the system have been considered.

In an $FeSO_4$-doped gel, the absorbed dose after exposure to ionising radiation can be determined from the measurement of certain parameters of the system, which undergoes a modification owing to the conversion of ferrous to ferric ions. The conventional method for the Fricke dosimeter reading takes advantage of the variation in the optical absorption in the visible spectrum, measurable by means of spectrophotometric instrumentation. Indeed, spectrophotometry provides a valid methodology because it is practical and highly reliable, and it is convenient in most circumstances. However, if a three-dimensional determination of the absorbed dose is required, more attractive parameters are the spin relaxation times of hydrogen nuclei in the aqueous solution. In fact, ferrous and ferric ions are both paramagnetic, but they cause a different reduction in the spin relaxation rates of protons. A linear correlation between absorbed dose and either transverse or longitudinal relaxation rate has been found. Hence, after a phantom made with $FeSO_4$-infused gel is exposed to ionising radiation, one can determine the three-dimensional distribution of absorbed dose by analysing the phantom by means of a Nuclear Magnetic Resonance (NMR) imaging system.

The first approach to the research has been made with the purpose of optimising the protocol for gel preparation and the modality of analysis of the dosimeter, in order to have,

is obviously a function of gel composition, is considerably affected by the gel preparation procedure. Hence, we have assembled a proper set-up (shown in Fig. 1) for gel preparation, which allows one to get dosimeters made up in the same conditions, in particular in regard to gel oxygenation and steam loss restraint.

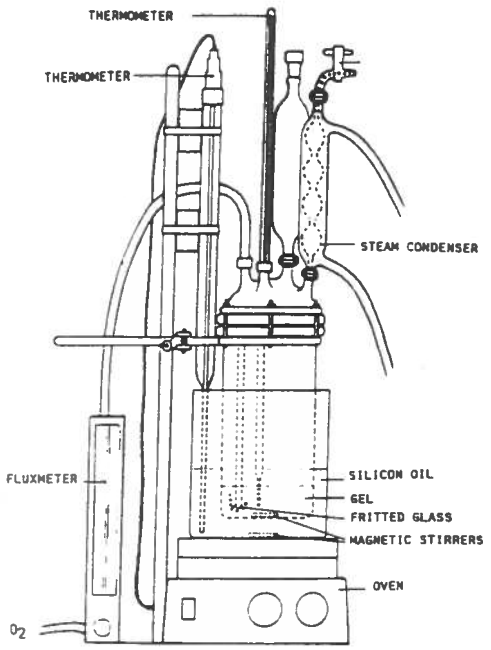

Figure 1. View of the apparatus for the dosimeter gel preparation.

For good result reproducibility, some care has to be taken. The dosimeter response is to be determined by comparison with a blank sample. In NMR analysis, a good result is achieved if the response R is defined as the difference between the relaxation rate measured in the irradiated sample and that measured, at the same time, in a non-irradiated sample from the same gel preparation:

$$R = (1/T)_{irr} - (1/T)_{blank} .$$

A non-negligible variation of relaxation rates in function of the time between gel preparation and irradiation, and of the time between irradiation and measurement has also been observed[(2)], but these time dependences have proved to have good reproducibility, and they may be therefore experimentally determined for the gel having the chosen composition, in order to evaluate convenient corrective factors to rectify the results of measurements.

A troublesome feature of ferrous-sulphate gels is ion diffusion and causes a progressive loss of localisation of the information about absorbed dose. This fact causes some limitations on

the utilizability of $FeSO_4$-infused phantom dosimeters for three-dimensional determination, because a prompt analysis after irradiation is necessary if good spatial resolution is required.

An investigation about ion diffusion has been made, utilising the gel having the composition optimised for gamma radiation. The gel was exposed to γ-rays through a thick lead screen with an open gap 4 mm wide. The dose distribution, as determined by means of TL dosimeters, had a Gaussian shape with a 5 mm FWHM. The NMR analysis of the gel 60 min, 140 min and 24 h after irradiation gave the results as shown in Fig. 2.

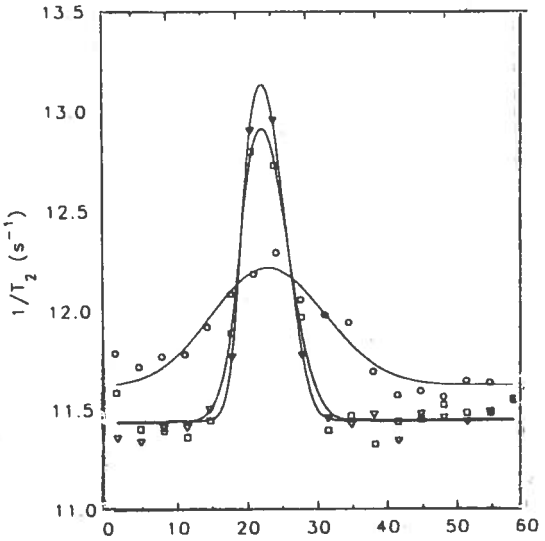

Figure 2. Relaxation time profiles along the cylindrical vials after irradiation in a slice 5 mm thick. The measurements are taken in slices 4 mm thick from the top to the bottom of the vials at various times after irradiation: 1 h, 2 h 20 min, 24 h.

Other secondary but not inconsequential effects are to be borne in mind in order to avoid misunderstanding of the results. The gel must be enclosed in sealed air-tight containers. If some air bubbles are left in the container, then oxygen absorption may take place and consequently an increase of the relaxation rates may occur. The release of impurities from the container walls, moreover, may cause a variation of relaxation times, inducing therefore wall-effects; so, the gel container material is to be properly selected. Finally, the gel temperature at the time of exposition has to be controlled, because a significant dependence of dosimeter response on the sample temperature during irradiation was revealed. This dependence was analysed in gels having two different compositions, and shown to have remarkably different entities for the two examined gels. It is therefore necessary either to inquire of the temperature dependence of the sensitivity of the dosimeter having the chosen composition, or to keep the samples at the desired uniform temperature at the time of irradiation.

In consideration of the above mentioned ion diffusion, and of the consequent necessity of performing a prompt NMR analysis after sample exposure, in order to avoid loss of localisation of 3-D information of absorbed dose, and furthermore in consideration of the fact that sometimes a rapid NMR analysis is not possible, we have suggested the technique of dividing the phantom into small fractions contained in an envelope, which brings a negligible (or at least

calculable) contribution to the results of measurements. Thus, we have verified the possibility of analysing small samples of the Fricke-infused gel. In particular, we have tested the feasibility of evaluating the relaxation rates when the gel dosimeter is contained in thin glass capillaries (1.1 mm internal diameter), because such containers would be suitable for an experiment with proton beams, which will be described in Section 5. For a first test, we have utilized a gel composed of Agarose in the amount of 1% of the final weight and ferrous sulphate solution in the amount of 50% of the final weight.

Some capillaries were exposed to 6 MeV photons, with a dose rate of 4 Gy/min, up to different doses. The samples were examined in a research NMR analyser (VARIAN) operating at 11.4 T and 500 MHz. The longitudinal proton relaxation rates $1/T_1$ were determined here, utilising an inversion recovery procedure. The results are shown in Fig. 3, where each point is obtained as a mean of 5 values.

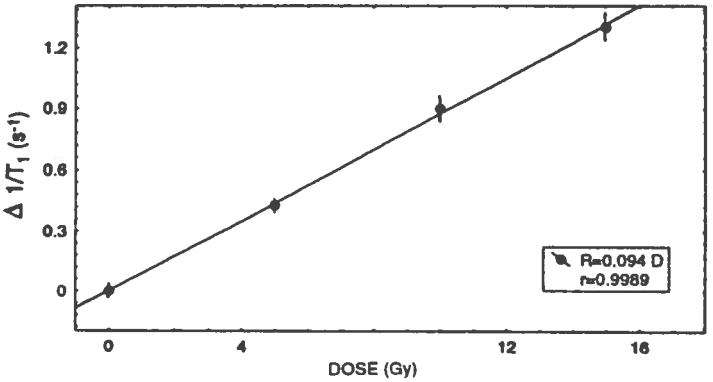

Figure 3. Response of the ferrous sulphate gel in capillary containers irradiated with 6 MeV photons and analysed by NMR measurements.

The standard analytical technique for dose determinations through the Fricke dosimeter utilizes a spectrophotometric readout. In fact, spectrophotometry provides a very convenient and precise technique. Therefore we have also tested our dosimeter-gel by means of spectrophotometric analysis, in order to verify the consistence and correctness of the results obtained from NMR analysis. To this end, we have utilised a 554 UV/VIS and an HP 8452A Diode-Array Spectrophotometer (Hewlett Packard). Ferric ions in sulphuric acid solutions induce, in the UV region, absorption peaks at short wavelengths, below or near 300 nm. Owing to spurious absorption effects at such wavelengths, an enhancement of the spectrophotometric measurement sensitivity is obtained by adding to the gel components a proper metal ion indicator which yields absorption in the visible spectrum. We have chosen Xylenol Orange ($C_{31}H_{28}N_2Na_4O_{13}S$), which shows a peak at 580 nm. The sensitivity of the dosimeter changes with the metal indicator concentration. Dosimeters containing different amounts of Xylenol Orange, irradiated to various doses, were analysed.

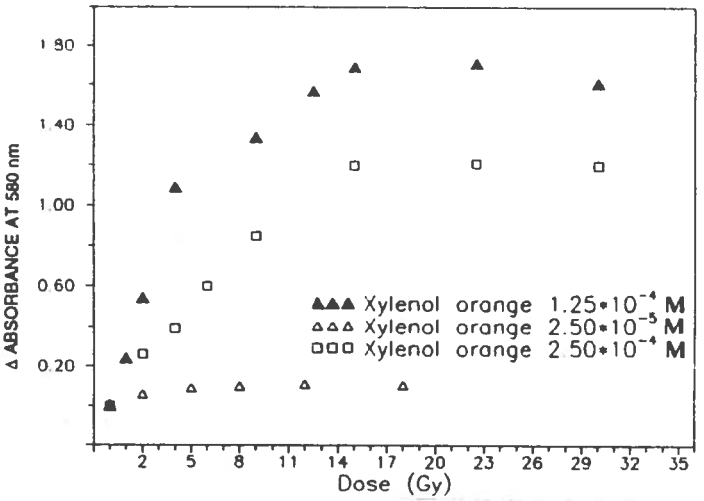

Figure 4. Optical absorption of gamma-irradiated dosimeter in 1-cm cells at 580 nm, as a function of radiation dose and Xylenol orange concentration.

Some results are shown in Fig. 4. The best characteristics as regards both sensitivity and linearity interval of the dosimeter are obtained with a Xylenol Orange concentration equal to $1.25 \cdot 10^{-4}$ M, and such a concentration was chosen in following experiments.

3. RESPONSE OF THE DOSIMETER TO GAMMA-RAYS

A broad experimental study has been made[1] of dosimeters exposed to a γ-ray field, in order to optimise the sensitivity of the system to such radiation. Sample exposures have been made in a 1400 Ci ^{137}Cs irradiator. The NMR analysis of gels has been made in a medical Magnetic Resonance Imaging system (Somatom Siemens). This analyser is a superconducting whole-body imager operating at 1.5 T and 63 MHz. Only the spin-spin relaxation rates $1/T_2$ were generally determined. In fact, the transverse relaxation rate has proved to give higher sensitivity than the longitudinal relaxation rate $1/T_1$. The spin-echo images were obtained employing a multi-echo sequence with 16 echoes. The characteristic times of the sequence were: echo times $T_E = (28 + 20n)$ ms where $n = 0,...,15$ and repetition time $T_R = 2.5$ s. Data elaboration was performed assuming a mono-exponential process, with a non-linear, least-squared, three-parameters algorithm.

In Fig. 5 a typical result of spin-echo fit is shown. The goodness of the fitting procedure is evident.

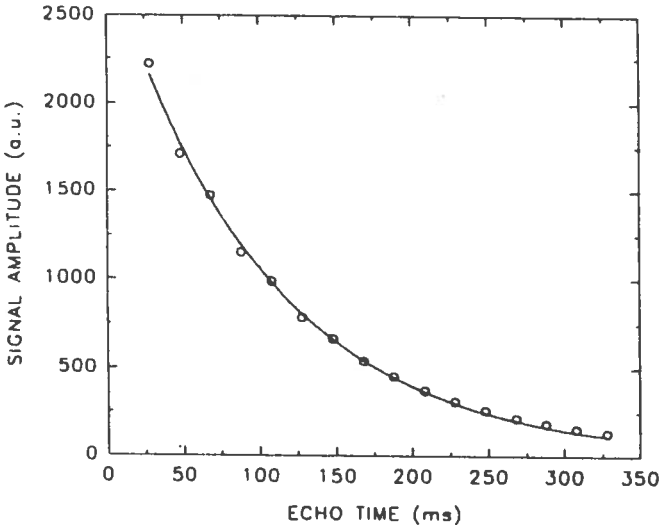

Figure 5. The spin-echo amplitude taken from measurements in a $FeSO_4$ Agarose gel, with a one-exponential three-parameters fit.

The highest sensitivity has been obtained from a dosimeter having the following composition: *ferrous sulphate solution* *1 mM* $Fe(NH_4)\,6H_2O$ *and* *50 mM* H_2SO_4 in the amount of 50% of the final weight

Agarose SeaPlaque $[C_{12}H_{14}O_5(OH)_4]_n$ in the amount of 1% of the final weight.

highly purified water H_2O in the amount of 49% of the final weight.

The dose-response curve slope of this gel results to be 0.2 s^{-1} Gy^{-1}. We have evaluated the G value of the dosimeter from the relation [2]:

$$G = (R/D)\ 9.64\ 10^9/\rho\ (R_b - R_a)\quad (Fe^{3+}\text{ ions per 100 eV})$$

were:

- R = dosimeter response (s^{-1})
- D = absorbed dose (Gy)
- R_a = relaxation rate increase per unit concentration of ferrous ion
- R_b = relaxation rate increase per unit concentration of ferric ion
- ρ = density (kg m^{-3}).

To estimate the value of $(R_b - R_a)$ we have utilised the experimental results of Prasad *et al.*[3] . In conditions similar to those of our NMR analysis, one has the values:

$R_a = 0.4\ s^{-1}\ mM^{-1}$ and $R_b = 10.2\ s^{-1}$ mM.

The density of the gel is 1076 kg m^{-3}. The ferric ion yield results to have the value:

G = 183 (Fe^{3+} ions per 100 eV absorbed energy).

This is a value about a factor 12 higher than the characteristic for the basic Fricke dosimeter. The dose-response curve shows good linearity up to about 35 Gy.

In Fig. 6 some experimental results showing the dosimeter response are presented. The results are obtained from relaxation rate measurements utilising five different sets of samples, i.e. samples from the same industrial batches. No temporal correction of the data has been made, but the time between preparation and irradiation was in the range 0-3 days, and the NMR analysis was made on the same day as the irradiation.

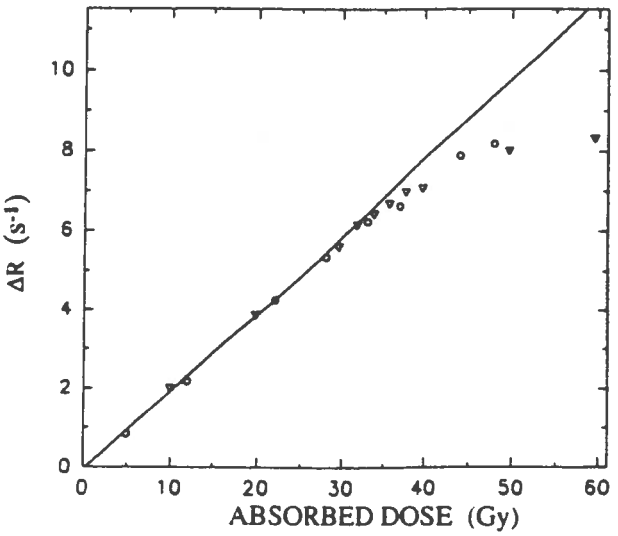

Figure 6. The dose-response curve of the $FeSO_4$ Agarose gel shows a good linearity up to abaut 35 Gy.

The tissue-equivalence of the dosimeter for γ-rays is also very good. In fact, the effective atomic number (photoelectric effect) results to be 7.80 for brain and 7.67 for the gel.

In conclusion, the gel having the above reported composition has proved to be a good dosimeter for three-dimensional determinations of absorbed dose in gamma radiation fields.

A gel with a different composition was analysed too, both with a research NMR analyser and with a spectrophotometer. The gel composition was that previously described, but augmented with 5 mM benzoic acid and 0.125 mM Xylenol Orange. Tissue-equivalence remains equally good: the effective atomic number (photoelectric effect) results equal to 7.74. We have verified the possibility of analysing small samples of the Fricke-infused gel. In particular, we have tested the feasibility of evaluating the relaxation rates when the gel dosimeter is contained in thin glass capillaries of 1.1 mm internal diameter. The capillaries were exposed in the ^{137}Cs irradiator, up to different doses. The samples were examined in a research NMR analyser (BRUKER AC-300) operating at 7.05 T and 300 MHz. In this high field, the water-proton relaxation in the dosimeter gives a very narrow signal, and therefore longitudinal relaxation times T_1 are better measurable than transverse relaxation times T_2. So, the longitudinal relaxation rates ($1/T_1$) were here determined, utilising an inversion recovery procedure. The NMR spin-lattice relaxation rates depend on field frequency, and in Fricke solutions the NMR sensitivity is lower for higher frequencies[4]. The dose-response curve slope results to be 0.006-s^{-1} Gy^{-1}. Gel contained in capillaries made with boro-silicate glass, 1 mm internal diameter, were examined with a Bruker AC-300 analyser, operating at 11.4 T and 300 MHz. The response of the dosimeter to the γ-rays of ^{137}Cs is shown in Fig. 7.

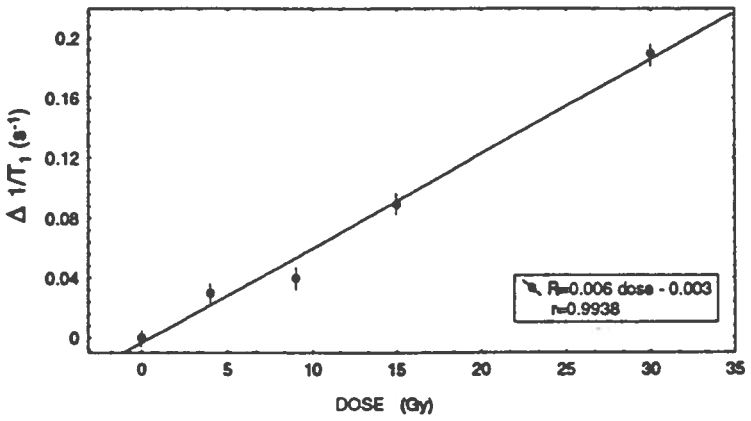

Figure 7. Response of the dosimeter to the γ-rays of ^{137}Cs.

Spectrophotometric analysis of the gel having above composition has also been made. In this case, the gel was contained in the cells (PMMA UV grade) proper for this instrument. In

Fig. 8 some absorbance curves are shown, obtained from gel samples (a) before and (b) after exposure to the γ-ray field.

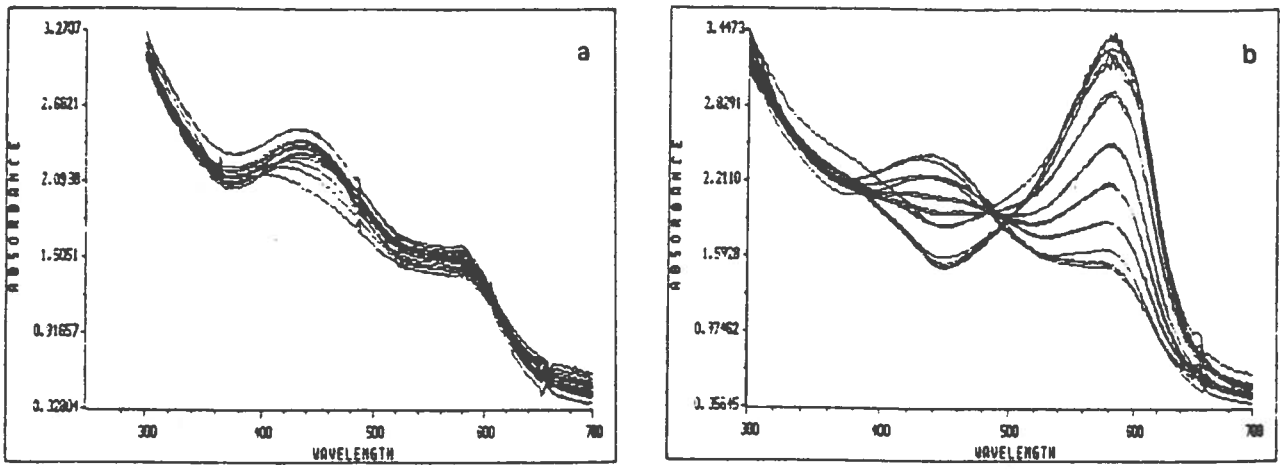

Figure 8. Response of gel added with a metal ion indicator and analysed by spectrophotometer. Absorption curves of (a) non-irradiated and (b) irradiated samples.

The presence of a well defined isosbestic point in the curves from samples irradiated at different doses testifies the equilibrium between two species. The absorbance at 580 nm is linearly correlated to the absorbed dose. Here we take response R of the dosimeter as the difference between the absorbance at 580 nm of the irradiated sample and that of a non-irradiated sample from the same gel preparation:

$$R = \Delta \text{ Abs } (580\text{nm}) = \text{Abs}_{\text{irr}} - \text{Abs}_{\text{blank}} .$$

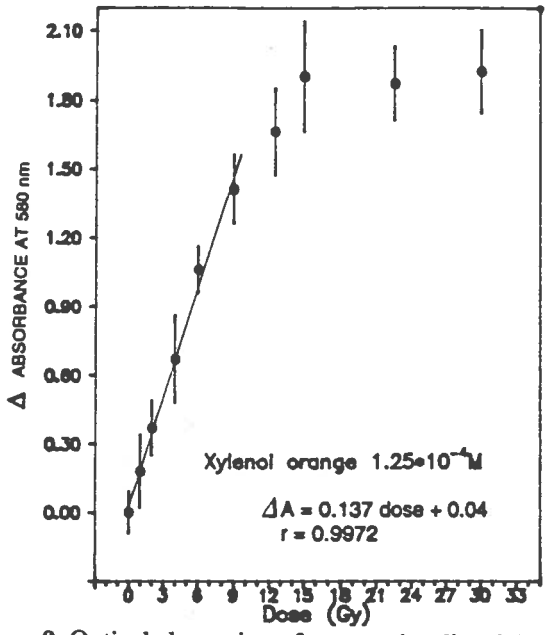

Figure 9. Optical absorption of gamma-irradiated dosimeter in 1-cm cells at 580 nm.

In Fig. 9, the response of the dosimeter to γ radiation is shown; the points are evaluated as mean of the values obtained from three measurements. The linearity appears to be good up to about 10 Gy. The sensitivity of the system is high. The minimum detectable dose, defined as the dose which produces a dose equal to three times the standard deviation (ICRU 22, 1972), was found to be equal to 1 Gy.

4. FERROUS-SULPHATE-DOPED AGAROSE GEL FOR B.N.C.T.

An investigation into the possibility of advantageously utilising a ferrous-sulphate gel to compose phantom-dosimeters for three-dimensional determinations of absorbed dose in B.N.C.T. has been performed[5].

In B.N.C.T., high concentrations of ^{10}B in tumours are achieved by means of tumour-seeking boron compounds. The therapy takes advantage of the high cross section (about 3840 b) of 10B for the reaction with thermal neutrons

$$^{10}B(n,\alpha)^{7}Li\ .$$

The heavy particles ^{4}He and ^{7}Li emitted in such a reaction have a high LET and moreover a short range in tissue ($\approx$10 μm), of the order of cellular dimensions. The released energy (about 2.4 MeV total energy) therefore produces selective destruction of cancerous cells. The absorbed dose in B.N.C.T. consists of the contribution of many radiation components, and if a localised ^{10}B accumulation is pursued, the spatial dose distribution is highly non-uniform.

In the design of a phantom to be utilised in the determination of absorbed dose in a field of thermal neutrons, particular attention has to be paid to tissue-equivalence. In fact, tissue-equivalence for thermal neutrons is a very critical problem, because such particles do not interact with atomic electrons, as photons and charged particles do, but with nuclei. The absorbed energy derives from the reaction products, and consequently in a tissue-substitute both the cross sections for thermal neutrons and the secondary particle spectra have to be similar to those of the tissue to be simulated. The only way to achieve this result is to realise a tissue-substitute with isotopic composition identical to that of tissue, at least as regards the isotopes that give the main contributions to the absorbed dose. Moreover, for a good equivalence the specific tissue of interest has to be simulated. Obviously, also the density of the substitute has to be near that of tissue.

In tissue, thermal and intermediate energy neutrons release very low energy. In the absence of ^{10}B, the main contribution to the absorbed dose comes from nuclear reactions with nitrogen and hydrogen:

$$^{14}N(n,p)^{14}C \qquad\qquad ^{1}H(n,\gamma)^{2}H\ .$$

In small volumes (less than 1 cm^3), the dominant contribution to the absorbed dose is due to protons (approximately 590 keV) emitted in the reaction with nitrogen. So, the percentage of N

is of fundamental importance. Photons emitted in the reaction with hydrogen, having an energy of 2.2 MeV, interact at a distance from the reaction site, and they appreciably contribute to the absorbed dose in relatively large biological objects (ICRU-26). Oxygen and carbon, which are the other main components of tissue, in the thermal and epithermal region of neutron energy play a very similar role as regards Kerma and, however, do not significantly contribute to the absorbed dose. Thus, for tissue-equivalence only the total percentage (C+O) may be considered. On the other hand, the percentage of N is of fundamental importance. In bone, the contribution of calcium is also to be taken into consideration.

	percentage by mass			
	H	N	C	O
Adipose tissue	11.4	0.7	59.8	27.8
Blood (whole)	10.2	3.3	11.0	74.5
Brain (grey/white matter 50:50 by mass)	10.7	2.2	14.5	71.2
Eye lens	9.6	5.7	19.5	64.6
Muscle(skeletal)	10.2	3.4	14.3	71.0
Frigerio gel	10.0	4.0	12.0	73.3
Frigerio liquid	10.2	3.5	12.3	72.9
Rossi gel	9.8	3.6	15.7	70.9
Goodman liquid	10.2	3.6	12.0	74.2

Table 1. The elemental mass fractions of H, N, C, and O for some body tissues and for some tissue-substitute.

In Tab.1 the elemental mass fractions of H, N, C and O for some body tissues and for some tissue-substitute (from ICRU 44, 1989) are reported.

The gel we have optimised for γ-radiation (hereafter named 1st gel) has good tissue equivalence for γ-rays but not for thermal neutrons, principally owing to its very low content of nitrogen. So, we have augmented the gel with a proper amount of the organic compound carbonyldiamide (*urea* CH_4N_2O from Fluka Chem. Corp.). In this work we have simulated brain tissue, because brain is the actual target of B.N.C.T. The composition of the gel (hereafter named 2nd gel) is the following:

ferrous sulphate solution	*1mM* $Fe(NH_4)\ 6H_2O$ *and 50 mM* H_2SO_4 in the amount of 50% of the final weight
Agarose SeaPlaque	[$C_{12}H_{14}O_5(OH)_4$] in the amount of 1% of the final weight
urea	[CH_4N_2O] in the amount of 4% of the final weight
highly purified water H_2O	in the amount of 45% of the final weight.

The elemental composition of the two gels is thus as repoerted below:

	PERCENTAGE BY MASS				
	H	N	C	O	others
1ST GEL	11.07	0.0013	0.31	88.52	0.1
2ND GEL	10.9	2.2	1.4	85.4	0.1

As one can see, the percentages by mass of H, N and (C+O) in the 2nd gel are very near to those in brain tissue, so that the tissue-equivalence of this gel for thermal neutrons is very good. For γ-rays the tissue-equivalence of both gels is equally good. Infact, the atomic number (photoelectric effect) is equal to 7.65.

Some dosimeters have also been prepared also utilising the 2nd gel augmented with 40 μg/g of ^{10}B, which is the quantity typically accumulated in tumours. The gel without boron exposed to thermal neutrons, even in fluences of the order of 10^{12}-10^{13} n/cm^2, absorbs a low dose, just for its tissue equivalence. The absorbed dose in tissue exposed to a thermal neutron fluence of 10^{12} n/cm^2 is equal to 0.201 Gy(6). The absorbed dose due to 40 μg/g of ^{10}B has been evaluated by means of the relation:

$$D = 1.602\ 10^{10}\ \sigma\ F\ N\ E\ \Phi \quad (Gy)$$

where:	D	is the absorbed dose in Gy
	$\sigma = 3.837\ 10^{-21}$ cm^2	is the interaction cross section
	$F = 4\ 10^{-5}$	is the ^{10}B fraction by weight
	$N = 6\ 10^{22}$	is the number of ^{10}B atoms per gram
	E = 2.28 MeV	is the energy released per event
	Φ	is the thermal neutron fluence in n/cm^2.

and thus we obtain for the absorbed dose per unit fluence:

$$D = 3.364\ 10^{-12} \quad (\text{Gy cm}^2)\,. \tag{1}$$

The response of the gel to γ-radiation has been preliminarily investigated by analysing various dosimeters after exposure in the ^{137}Cs irradiator. All samples were contained in small cylindrical Teflon vials, with 0.5 mm thick walls, 22 mm internal diameter and 45 mm height. Both the dosimeters (i.e. with and without ^{10}B) have been shown to have the same γ-sensitivity. The dose-response curve slope has resulted to be equal to 0.065 s^{-1} Gy^{-1} . This value is lower than that obtained with 1st gel dosimeters optimised for γ-rays, but it is still higher than that of the standard Fricke dosimeter. In contrast, the linearity of the response is good up to 50 Gy, that is for a wider range than that of the previous gel, as one might expect, considering that a lower ion conversion allows a wider linearity.

We have analysed dosimeters made with both borated and non-borated gel, exposed to various thermal neutron fluences in the thermal column of the TRIGA MARK II nuclear reactor of L.E.N.A. (Pavia-Italy). The results are shown in Fig.10. The dosimeters analysed were all identical in shape and composition, except for boron contents, and all samples that were irradiated up to the same fluence were subjected to the same exposure conditions. In the gel-dosimeters without boron, the response was due to thermal neutrons and to γ-rays from reactor and from short-life activation of sample containers and holders.

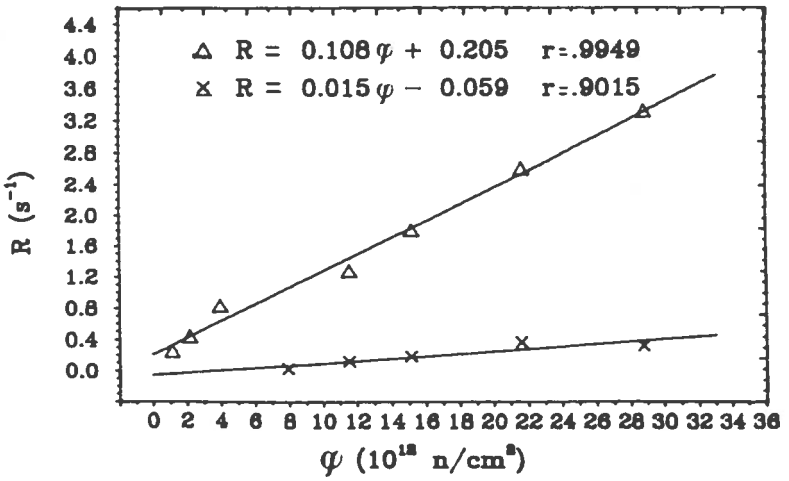

Figure 10. Response of gels (Δ) with and (x) without ^{10}B to (n_{th}, γ) mixed fields, versus thermal neutron fluence.

We have made differential measurements with borated and regular gels exposed in the same thermal column position and in the same fluence. The difference between the slopes of the dose-response curves obtained from the dosimeters with and without boron is uniquely

associated to the absorbed dose due to ^{10}B. From the slopes in Fig 10 we obtain that the response of borated gel per unit fluence is $R_B/\Phi = 0.108\ 10^{-12}$ (s^{-1} cm^2) and that of the regular gel is $R/\Phi = 0.015\ 10^{-12}$ (s^{-1} cm^2). So

$$0.093\ 10^{-12}\ (s^{-1}\ cm^2)$$

(i.e. 86% of the total) is attributable to the absorbed dose due to ^{10}B. The remaining 14$ of the response, includes contributions from thermal neutrons in tissue, fast neutrons, reactor background and activation of the materials of the containers and holders. By comparing the experimental value (2) with the calculated dose (1) due to ^{10}B, the sensitivity of the borated dosimeter to the secondary particles produced by thermal neutrons reacting with ^{10} has resulted to be equal to R = 0.028 (s-1 Gy^{-1}). This value is lower than that obtained for γ-rays, reported above, but it is sufficient to obtain satisfactory dose evaluations.

The net difference in the slopes of the responses of borated and non-borated gels have confirmed the feasibility of the dosimetric method, and have encouraged the continuation of the set up of the dosimeter and experimentation on larger phantoms simulating real situations, exposed to epithermal neutron fluxes.

The results reported above were obtained with gel samples contained in small cylindrical vials. Than the work was dedicated to investigate into the homogeneity of response inside large phantoms and to define a modality for determining spatial dose distributions and isodose curves.

Phantoms consisting of the borated gel were made up in form of cylinders having 8 cm diameter and 15 cm height, enclosed in Teflon containers 2.3 mm thick. Teflon was chosen also for sample holders exposed in the thermal column of the reactor, in order to reduce the contribution to the dosimeter response coming from activation of container and holder materials. NMR imaging of unexposed samples was done, to check gel uniformity and moreover to see if some systematic differences in the relaxation rate are evident. The relaxation rates $1/T_2$ measured at various positions in the phantom are uniform within 1%, and no systematic effect has been evidenced. The obtained images however show that the system is very delicate and sensitive to strokes and to quick changes of orientation of the phantom.

A few phantoms have been exposed in the uniform γ-radiation field of the ^{137}Cs biologic irradiator and then analysed, in order to verify if some variation in the dosimeter sensitivity from the middle to the periphery of phantoms is observable. In fact, a dependence of Fricke-infused gel sensitivity on the cooling rate after gel preparation has been observed by some authors and, obviously, in a wide phantom the difference in the cooling rates from middle to edge may be not

negligible. However the effect was found to be weaker when Agarose SeaPlaque was utilised as a gelling agent. From the NMR imaging of uniformly irradiated phantoms we have seen that no such an effect is noticeable out of the previously discussed error of the relaxation rate measurement.

In consideration of the fact that a not negligible dependence of the dosimeter response on the sample temperature at the time of irradiation was found, and moreover that the phantoms in the thermal column of the reactor may undergo a temperature variation, with a gradient from the middle to the edge of the sample, we have irradiated up to 6 Gy in an uniform γ-field a phantom that was previously dipped in hot water, to give rise to a not negligible temperature gradient. When the phantom was irradiated, his temperature, measured in another identical phantom subject to the same thermal treatment, was of 4 °C in the middle and of 22 °C at the edge. After exposure, the phantom was left to reach an uniform temperature before NMR analysis.

In the NMR image of the phantom, shown in Fig. 11, the temperature effect is visible. The clearest is the area, the highest is the value of relaxation rate, and consequently the sensitivity of the gel. From the edge to the middle of the phantom the sensitivity varies from 0.083 s^{-1} Gy^{-1} to 0.065 s^{-1} Gy^{-1}. The relative change in the gel sensitivity due to temperature variation results to be equal to about 1.5 % per °C.

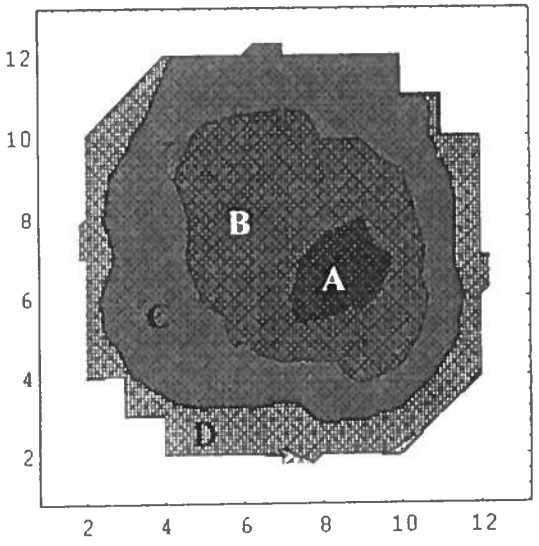

Figure 11. NMR image of the phantom-dosemeter: the temperature effect is visible.

Finally, a cylindrical phantom 8 cm diameter 15 cm height, consisting of the Fricke-infused gel containig 40 μg/g ^{10}B, was exposed in the thermal column of the TRIGA MARK II reactor. After three hours the NMR imaging of the phantom has been done. In Fig.12 an image of the phantom is shown. The isodose drawings have irregular shapes because, owing to the low sensitivity of the dosimeter to thermal neutrons, the spurious effects above exposed are not hidden. No detailed considerations on such shapes are here done, because the information about the spatial distribution of thermal neutrons in the thermal column is scanty.

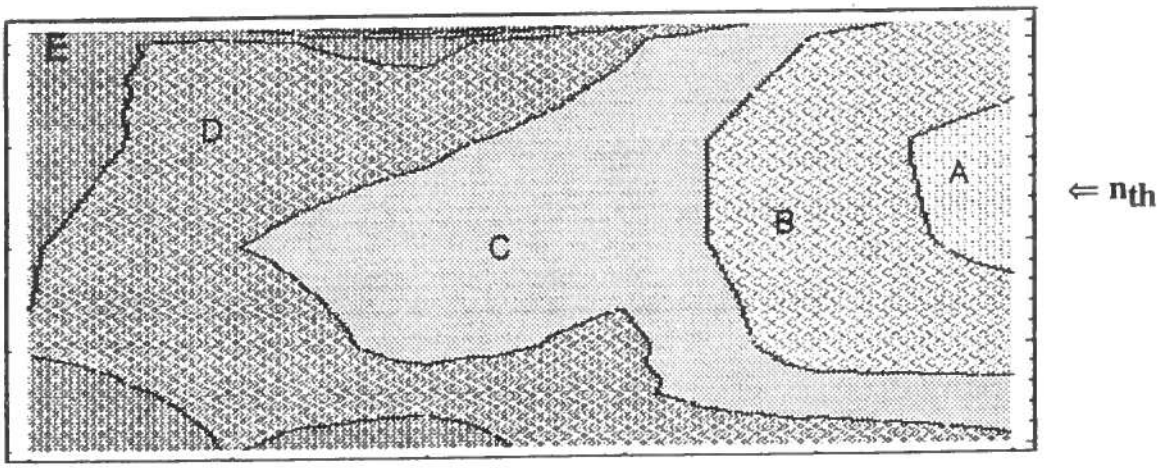

Figure 12. Imaging of a cylindrical borated gel phantom exposed in the thermal column of the reactor. The resulting dose values are: A 26-28 Gy, B 24-26 Gy, C 22-24 Gy, D 20-22 Gy, E 18-20 Gy.

From the fluence data at the central line of the reactor channel, however, a good accord was found between the relaxation rate values in the phantom an the sensitivity to thermal neutrons measured with small vials containing the same boronated Fricke-gel.

5. - RESPONSE OF FRICKE-INFUSED GEL DOSIMETERS TO PROTONS AND DEPTH-DOSE PROFILE DETERMINATIONS

We have investigated the feasibility of utilising the Fricke-infused Agarose gel for depth-dose profile determination in tissue exposed to a proton beam.

Protons, and in general heavy charged particles, offer advantages in radiotherapy. In fact, the low scattering and straggling events and the high ionisation near the end of particle tracks (Bragg peak) enable high doses to be delivered in tissue at depths of many centimetres, while maintaining a low entrance dose. Moreover, the therapeutic efficacy of such particles is higher than that of more conventional radiation.

The Bragg peak of monoenergetic proton beams is relatively sharp and, in order to obtain a uniform dose in a tumour, a convenient spread out in depth is obtained by modulating the energy of the beam. Measurements of unmodulated Bragg peaks for various energies are therefore necessary to correctly define the parameters of the beam. Peak shape and depth are generally determined by detecting protons emerging from tissue-equivalent absorbers of

different thickness. A precise determination of the shape of the resultant modulated Bragg peak is necessary for a good planning of therapy. So we have checked the feasibility of depth-dose profiling by NMR analysis of a dosimeter gel.

A shortcoming of ferrous-sulphate gels is ion diffusion; this causes a progressive loss of localisation of the information on the absorbed dose. This fact causes some limitations on the utilizability of $FeSO_4$-infused phantom dosimeters for three-dimensional determination, because a prompt NMR analysis after irradiation is necessary if good spatial resolution is required. In consideration of such an ion diffusion, and furthermore of the fact that sometimes a prompt NMR analysis after sample exposure is not possible, we have suggested the technique of determining the depth-dose profile by analysing the response of gel contained in thin capillaries pierced through tissue, at increasing distances from the surface. The capillary material brings a negligible, or at least calculable contribution to the results of the measurements. Thus, we have verified the possibility of analysing small samples of the Fricke-infused gel. In particular, we have tested the feasibility of evaluating the relaxation rates when the gel dosimeter is contained in thin glass capillaries of 1.1 mm internal diameter. We have utilized the gel containing Xylenol Orange (in the amount of 01.25 10^{-4} M) in order to make also spectrophotometric measurements. The capillaries were exposed in the ^{137}Cs biological irradiator, up to different doses. The samples were examined in a research NMR analyser (BRUKER AC-300) operating at 7.05 T and 300 MHz. The longitudinal proton relaxation rates $1/T_1$ were determined utilizing an Inversion Recovery procedure, and the response to γ-rays, as reported before, is equal to about 0.006 s^{-1} Gy^{-1}.

In a first experiment, done to test the dosimeter sensitivity to protons, gel was poured into the small PMMA UV containers proper to the spectrophotometer. The vials have a rectangular section, with 1 cm optical path: the gel thickness is of 3 mm. Two arrays of 12 vials were settled in front of the beam. Protons are stopped in the first array, and therefore the response of the second array of dosimeters gives information about the γ-background in each vial position. To have a further control about proton and γ-ray contributions to the radiation field in the site of samples, also thermoluminescent dosimeters (TLD-700 from Harshow) were placed near vials, both in front of the first array and behind the second one. Proton expositions have been made at the CYPRIS cyclotron (Pisa-Italy). The system was placed at a distance of about 10 cm from the cyclotron window, and exposed to 1 μA beam for 1 s, because these are the

minimum available current and the minimum possible time. The proton energy on samples was of 15.5 ± 0.6 MeV.

In Fig. 13 the gamma-equivalent dose measured by means of the TLDs-700 is reported. We can see that the beam was highly disomogeneous, and that some dosimeters have undergone a very high dose. In fact, in the corresponding gel samples some bubbles were visible and, as a consequence, the spectro-photographic analysis has revealed a decrease of absorbance instead of an increase, as one can see from the results reported in Fig.14.

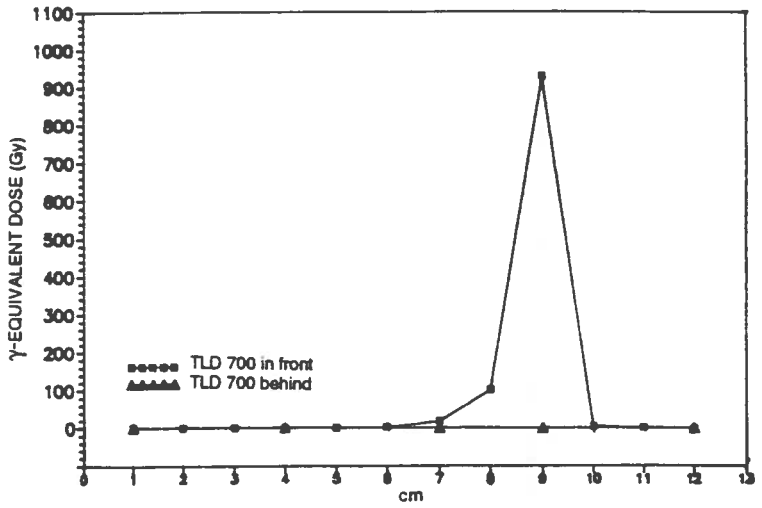

Figure 13. Transversal profile of the proton beam, measured by an array of thermoluminescent dosimeters (TLD-700).

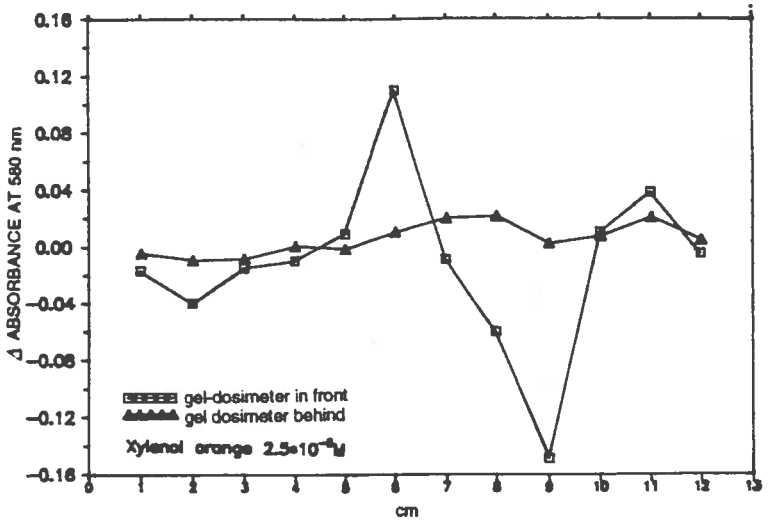

Figure 14. Transversal profile of the proton beam, measured by an array of gel dosimeter.

Therefore, to obtain a drastic reduction in the proton flux on samples, and moreover to obtain a flattening of the proton distribution, we have placed near the cyclotron window a stopper-scatterer system. The system is composed of a nylon stopper 3 mm thick, whose shape was chosen on the basis of the shape of the radiation damage figure visible on the cyclotron window, and of an Al scatterer 0.057 mm thick, whose role is that of flattening the proton dose

distribution on the exposition area, as it is schematically shown in Fig. 15. To promptly verify the efficacy of the system and to correctly locate samples, a check has been done by irradiating photographic paper. The image on the paper was satisfactory in the region of interest. The proton energy on the sample is now equal to 13.5 MeV.

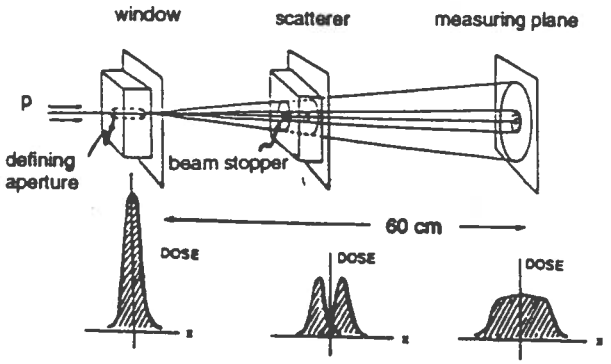

Figure 15. View of the flattening system.

Two arrays of gel dosimeters and of TLDs have been exposed in the same configuration as previously described, and the results obtained from the analysis of samples are shown in Fig. 16 and in Fig. 17.

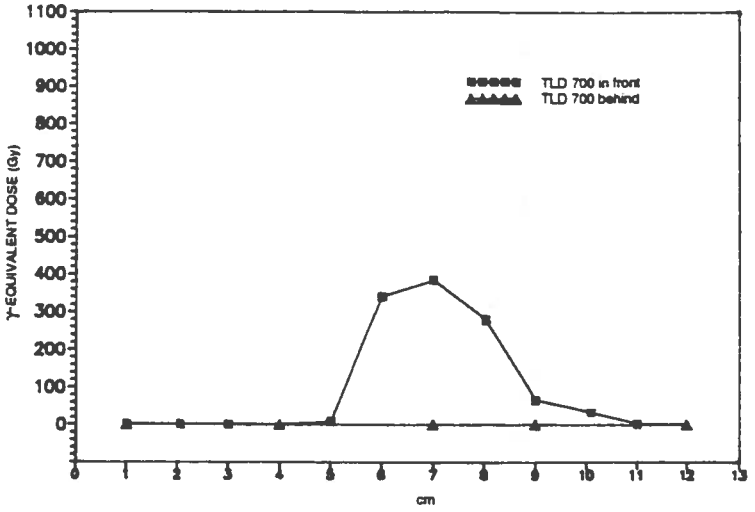

Figure 16. Transversal profile of the proton beam, exiting from the flattening system, measured by an array of thermoluminescent dosemeters (TLD-700).

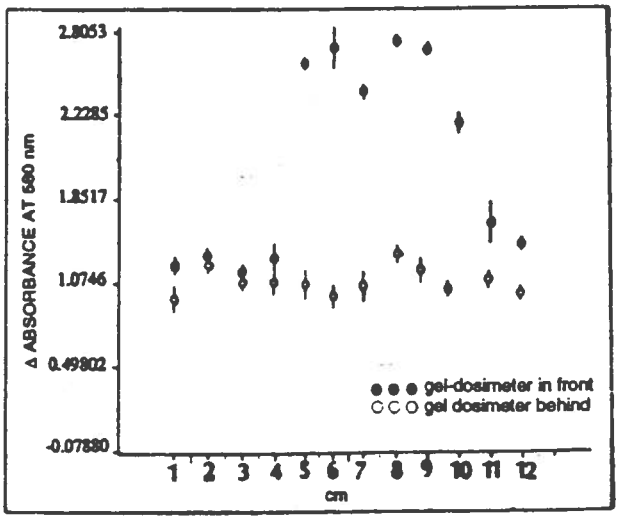

Figure 17. Transversal profile of the proton beam of the dosimeter gel analysed from the response of spectrophotometer.

Correlating the spectrophotometric results to the dose values obtained by means of TLDs (that is γ-equivalent dose) the sensitivity of the system to protons results to be equal to 0.19 Gy^{-1}, higher than the sensitivity to γ-rays that was equal to 0.13 Gy^{-1}. However, we have done no correction for the sensitivity of TLD-700 to proton, because neither from literature nor from our studies on thermoluminescent dosimeters some conclusive results are drown.

Two Plexiglas phantoms, with a rank of capillaries placed at increasing distances from the front surface, were exposed to the 13.5 MeV proton beam. The capillaries were then inspected in the NMR analyser. The results are shown in Fig. 18, where each point is obtained as a mean of two values.

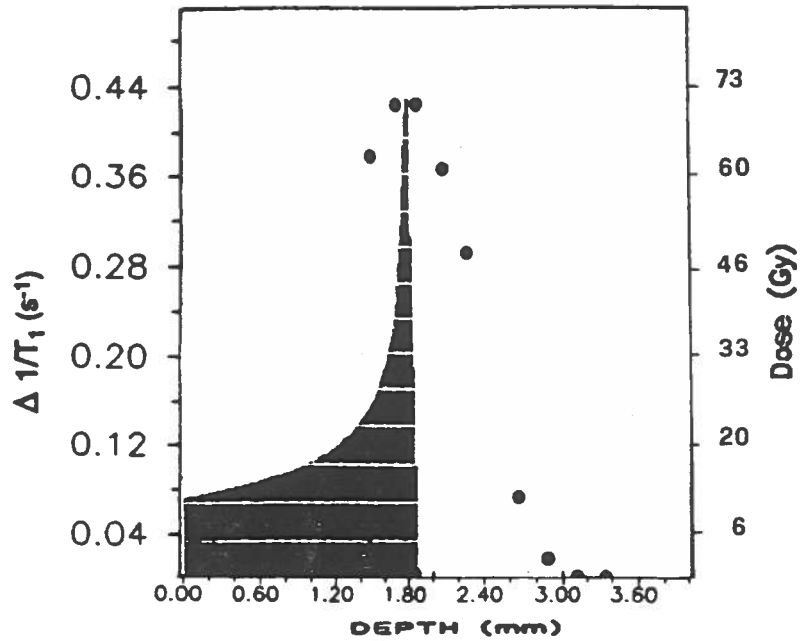

Figure 18. Response of the dosimeter gel in capillary containers located at increasing depths in plexiglass exposed to a 13.5 MeV proton beam.

In the figure also the energy loss in Plexiglas as evaluated by mean of the program TRIM is reported. the high precision of the obtained position of the Bragg curve maximim is evident.

A computer program has also been done by us, in order to evaluate the energy loss in the experimental conditions, that is in gel contained in glass capillaries placed in the Plexiglas phantom. The results are shown in Fig. 19, where the represented curves are: *a)* (solid line) specific energy released in Plexiglas by 13.5 MeV protons as a function of depth, and *b)* (dotted line) energy released in a gel dosimeter enclosed in glass containers with square section, 1 mm internal side, 0.2 mm thickness, located at increasing depths in Plexiglas.

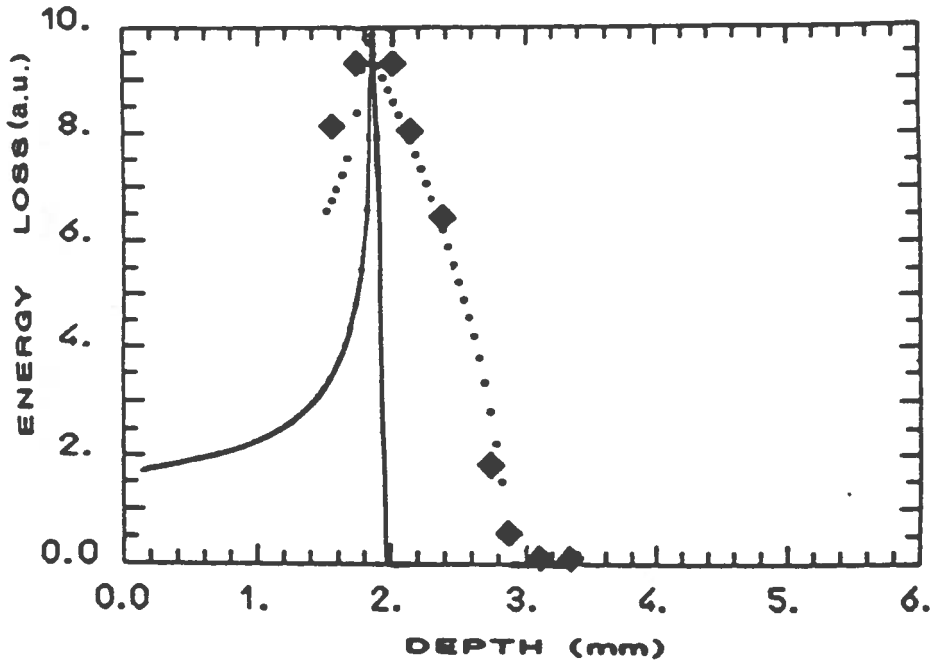

Figure 19. Depth-dose profile obtained from 13.5 MeV protons in plexiglass:
♦ Experimental points, — Computed Bragg curve, ... Computed loss energy in the dosimeter.

These results confirm the potentiality of the technique. In fact, the Bragg peak position is obtained within a tenth of a millimeter uncertainty, and the widening in the ramps is within 1 mm. This is an intrinsic characteristic of the dosimetric system, and the precision of measurements is the same, for whichever proton energy.

Moreover, we have also tested the response of the dosimeter gel to protons also by means of spectrophotometric analysis, in order to verify the consistence and correctness of the results obtained from the NMR analysis. To this end, we have analysed with the UV/VIS Diode-Array Spectrophotometer the gel added with Xylenol Orange ($1.25 \cdot 10^{-4}$ M). We have analysed samples both exposed to gamma and to proton radiation: the good agreement of these results with those obtained by NMR analysis are a further verification of the validity of the method.

CONCLUSIONS

The promising results obtained with the described dosimeter, in particular for 3-D dose determination in B.N.C.T. and for depth-dose profiling in proton therapy, they encourage us to continue the research with the aim of removing the difficulties (such as ion diffusion) and improving the dosimeter, eventually by studying a different kind of chemical dosimeter with better characteristics.

ACKNOWLEDGEMENTS

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