

POLYMER GEL DOSIMETRY APPLIED TO β PARTICLES, ELECTRONS AND 300 KV X-RAYS.

**Thesis submitted for the degree of
Doctor of Philosophy
at the University of Leicester**



by

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Polymer Gel Dosimetry Applied to β Particles, Electrons and 300 kV x-rays

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Abstract

Polymer gels were used with magnetic resonance imaging (MRI) to measure three-dimensional absorbed dose distributions for beta particles, electron and x-rays beams that are used in radiotherapy. The manufacturing processes and calibration procedures for two dosimeters (hypoxic PAG and normoxic MAGIC gels) were investigated. The response of both gels was energy independent over a range of electron and photon energies commonly used for radiotherapy. However, dose response of both gels was dependent on the temperature at the time of MR scanning, while MAGIC was also dependent on the temperature at the time of irradiation, which had not been previously reported. Results suggest that MAGIC gel is superior to PAG, since it is easier to manufacture and unaffected by oxygen diffusion through wall materials.

The potential usefulness of both types of gel in different areas of radiotherapy was studied, including vascular brachytherapy. Results were compared with doses measured using radio-chromic film, confirming that dose distributions for vascular brachytherapy sources with a high dose gradient can be measured using PAG. However, because of the disadvantages of the gel manufacturing process and the need for access to a high-resolution scanner, it was concluded that radio-chromic film would be the method of choice for routine quality assurance in brachytherapy.

PAG and MAGIC gels were also used for dosimetry across the junction of 6MV photon and 12MeV electron fields that are often used in radiotherapy. Different photon field configurations were studied, and dose profiles were measured. For each configuration either significant "hot" or "cold spots" were measured, with good agreement between the MAGIC and PAG and radio-chromic film.

This work has confirmed the usefulness of gel dosimetry in radiotherapy in general, and in beta and electron dosimetry in particular. In addition, these studies have quantified the advantages of normoxic gels over the hypoxic PAG.

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Statement of originality

The work presented in this thesis is original and unless otherwise stated in the text or by reference has been performed by myself. This is my own composition, and no part of this thesis has been submitted for another degree in this or any other university. Some of the material contained in this thesis has been presented at different conferences and one paper has been accepted for publication and another two are in preparation. These are:

1. Amin M.N., Horsfield M.A., Dunn M., Harding P.J., and Bonnett D.E. Investigations of a polyacrylamide gel dosimeter with high resolution MRI for dosimetry of a high dose rate beta source for intravascular brachytherapy. Proceedings of DOSGEL 2001 2nd International Conference on Radiotherapy Gel Dosimetry, Brisbane, Australia, Nov.2001: 133-135.
2. Amin M.N., Horsfield M.A., Dunn M., Harding P.J., and Bonnett D.E. Investigations of a polyacrylamide gel dosimeter with high resolution MRI for dosimetry of a high dose rate beta source for intravascular brachytherapy. Proceedings of the UK radiological congress, BJR congress series, p-73; 2002.
3. Amin M.N., Horsfield M.A., and Bonnett D.E. Investigation of the properties of the MAGIC gel dosimeter: Initial results. Proceedings of the annual scientific meeting of the Institute of Physics and Engineering in Medicine. 79-80. 2002
4. Amin M.N., Horsfield M.A., and Bonnett D.E. On the use of polymer gels for investigating abutting photon and electron fields in the treatment of head and neck cancers. 8th EFOMP congress, Eindhoven, The Netherlands. May 20-23; 2003. Physica Medica XIX(1): p73; 2003.
5. Amin M.N., Horsfield M.A., Bonnett D.E., Dunn M.J., Poulton M., and Harding P.J. A comparison of polyacrylamide gels and radio-chromic film for source measurements in intravascular brachytherapy. Accepted for publication in the British Journal of Radiology.

Abbreviations

BANANA	Bis, Acrylamide, Nitrous oxide, ANd Agarose
BANG	Bis, Acrylamide, Nitrogen, and Gelatin
BNCT	Boron neutron capture therapy
CP	Carr Purcell
CPMG	Carr Purcell Meiboom and Gill
CT	x-ray computed tomography
EPI	Echo planar spin echo
FAX	Ferrous-Agarose-Xylenol orange
¹⁸ FDG	Fluorodeoxyglucose labelled with Fluorine-18
FID	Free induction decay
FOV	Field of view
FSE	First spin echo
FT	Fourier transform
HDR	High dose rate
IMRT	Intensity modulated radiotherapy
LDR	Low dose rate
LET	Linear energy transfer
MAA	Methacrylic acid
MAGIC	Methacrylic and Ascorbic acid in Gelatin Initiated by Copper
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MSE	Multiple spin echo
MT	Magnetization transfer
NEX	Number of excitation
NMR	Nuclear magnetic resonance
NMV	Net magnetization vector
OCT	Optical computed tomography
PAG	Polyacrylamide gel
PET	Positron emission tomography
R ₁	Longitudinal relaxation rate
R ₂	Transverse relaxation rate
RF	Radio frequency

ROI	Region of interest
SE	Spin echo
SIE	Siemens image file format
SNR	Signal to noise ratio
SOBP	Spread out Bragg peak
SSD	Source to surface distance
T ₁	Longitudinal relaxation time
T ₂	Transverse relaxation time
TE	Echo time
TI	Inversion time
TL	Thermoluminescent
TLD	Thermoluminescent dosimeter
TR	Repetition time
UNC	University of North Carolina

Chapter 1

Developments in Radiotherapy

1.1 Introduction

The earliest man-made radiation sources were x-rays, discovered in the late evening of 8 November 1895 by the German Physicist Wilhelm Conrad Roentgen [Dam 1896]. Soon after the discovery, workers in Austria, Germany and then the USA began to use this radiation in the treatment of malignant tumours of different patients. This was referred to as radiotherapy. In 1896, a portable x-ray set was made in the USA [Webb 1988]. Shortly after the discovery of x-rays, Henry Becquerel discovered radioactivity in 1898, adding a new dimension to the application of radiation in physics, chemistry, biology and medicine. The isolation of radium by the Curies [Beiser 1987] was one key to this development, as was the improvement of the technology associated with x-ray production. In 1925, the International Committee on Radiological Units (ICRU) was set up to define and measure radioactive quantities. During the early years of the 20th century there was no established treatment planning. In those early days, machine energies were low and consequently the beam penetrating power was also low; therefore, the maximum dose was absorbed by the skin. In the early 1950s, the use of cobalt radiotherapy sources began; these sources contained several kilocuries of ^{60}Co , and more complex treatment planning developed. Later, high energy linear accelerators began to replace the cobalt-60 machine as the main treatment unit, this was made possible by the technology developed for radar.

In the 1950s, 1960s and, early 1970s the relative/absorbed dose was usually calculated at a single point inside the patient, but now this has changed. Tables of percentage depth doses were created by direct measurement of beam attenuation in water, corrections were made for field size, blocks and distance to the body surface and computation proceeded using reference tables and simple multiplication of the appropriate factors [Johns 1983]. With these methods, it was very laborious to calculate the dose distribution over a cross-section of the patient. For a single patient, it might be take many hours to compare several beam configurations.

The availability of the computer was a great help in radiotherapy treatment planning and it dramatically changed the radiotherapy treatment planning system. The first computerized planning systems appeared in the late 1950s [Tsien 1955], with development continuing into

the early 1960s [Van de Geijn 1965, Sterting 1964]. As computers became cheaper and faster, more sophisticated calculational algorithms were employed, factoring in the influence of variable tissue density, (e.g. lung) on the dose distribution [Batho 1964, Sontag and Cunningham 1978]. By the mid 1970s, computerized treatment planning for a single slice was the worldwide standard [Allen et al 1988]. At around this time x-ray computed tomography (CT) and magnetic resonance imaging (MRI) were being developed. In the 1990's there were further developments to radiotherapy machines, such as multileaf collimation, and this aided the development to what is known as conformal radiotherapy. Prior to this conformal therapy could only be achieved with leadblocks. Conformal therapy allows the shaping of the irradiated region precisely to the tumour volume, sparing more of the surrounding healthy tissue. Dynamic treatment techniques, stereotactic multiple beams and intensity modulated radiotherapy (IMRT) based on inverse planning [Brahme et al 1990] are currently being used [Boyer 1998]. Conformal and intensity modulated radiation therapy techniques are currently being developed, with a variety of tumour types being treated in many different anatomical sites [Webb 1997, Verellen et al 1997, Alheit et al 1999, Dearnaley et al 1999, DeNeve et al 1999]. Patient complications can be minimised by using these methods, resulting in the potential for improved treatment results and a greater probability of cure, particularly if there is an accompanying escalation of the prescribed dose.

1.2 CT Based Treatment Planning

Cancer is a major cause of mortality in the world. Overall, 30% patients with cancer are cured and return to a normal life [Webb 1988], and radiotherapy has an important role to play in this process.

Radiation therapy for malignant disease is complex and involves many steps. It begins with patient diagnosis and continues to treatment and carries through with on-going follow-up. One crucial step in this process is the determination of the location and extent of disease relative to adjacent critical normal tissues. The normal organs that surround a tumour limit the radiation dose that can be given because of their inherent and organ-dependent radiosensitivity. If this radiation tolerance were not taken into account when planning treatment, permanent damage to normal tissues would result.

In the early use of radiation, localisation of a tumour and adjacent sensitive organs within the body was carried out using orthogonal radiographs. All available patient data, i.e. clinical,

surgical and radiological, are taken into account when determining the volume for treatment, together with a knowledge of the natural history of the tumour and likely routes of microscopic spread. The limitations of the conventional process were due to the difficulty in transcribing data into the transverse plane required for dosimetry. Before treatment was initiated, the treatment plan needed to be confirmed by an imaging procedure to ensure that the beams traversed the desired anatomical volume and correlated accurately with respect to critical structures. The computerized tomography (CT) scanner has made an important contribution to these components of the radiation therapy process. The availability of CT scanners in the late 1970s led to major improvements in the radiation therapy planning process. The cross-sectional images given by these diagnostic techniques provide a wealth of anatomical data and are ideally suited for planning purposes. The application of CT scanning to radiation therapy lies in four major areas.

- (a) **Diagnosis:** As a diagnostic tool, the CT scanner provides qualitative information about irregularities within tissue structures which can be assessed by the radiologist for the extent and stage of disease. This is information required by the radiation oncologist to decide the treatment modality, technique, and prescribed dose.
- (b) **Tumour and normal tissue localization:** With a diagnosis of malignant disease, the radiation oncologist needs detailed quantitative information about tumour extent and intervening or adjacent normal tissues. This allows for detailed decisions about field sizes and beam configurations in order to maximize tumour dose while minimizing the dose to critical normal tissues.
- (c) **Density data for dose calculation:** The images from CT scanners are easily converted to relative electron densities, which are necessary for accurate dose calculations. Thus the CT scan not only provides information on external contours and internal structures but, in addition, it provides detailed density information, which can be used for dose calculations. CT scans also supply quantitative information about tissue inhomogeneities [Geise et al 1977, Kijewski et al 1978]. Several workers [Parker et al 1979, Cassell et al 1981, Elder et al 1995] have investigated the incorporation of the CT number directly into the treatment planning program in order to make inhomogeneity corrections, and this is now commonly incorporated into modern planning systems. ✓

- (d) Treatment monitoring: Follow-up CT images either during or after treatment afford a means of assessing tumour regression or recurrence, or normal tissue damage.

The clinical impact of CT on the therapy planning process is now well established [Goitein 1982, Brahme 1988]. Various studies have indicated modifications in 30-80 % of a select number of conventional non-CT treatment plans because of the additional information provided by CT. It is also recognized that some 10-40 % of all radiation therapy patients might benefit from CT scanning for therapy planning. Furthermore, a theoretical estimate indicates that the widespread use of CT planning could improve the local control probability by 6 per cent with an estimated 3.5 per cent increase in 5-year survival rates [Goitein 1982]. CT for therapy planning has been used for the majority of malignancies throughout the human body.

In addition to improvements in conventional two dimensional treatment planning, CT provides volumetric information well suited to more sophisticated three-dimensional treatment planning. True conformal therapy with complex shielding, moving fields, or multi-leaf collimators would not be possible without the three-dimensional information provided by CT. Without use of the CT scanner, the necessary accuracy in dose delivery would not be achievable.

1.3 MRI Based Treatment Planning

Nuclear Magnetic resonance (NMR) was discovered independently by Bloch et al [Bloch et al 1946] and by Purcell et al [Purcell et al 1946]. Magnetic resonance imaging continues to show improvement as an imaging modality for the assessment of malignant disease, particularly for sites such as the central nervous system, brain, head and neck, prostate, and lymph nodes. CT images often fail to differentiate unambiguously between tumour and normal tissue, but MRI provides excellent soft tissue contrast [Gibbs et al 1997]. Clinical experience with MRI has grown rapidly, and optimal pulse sequence design techniques are improving the ability to discriminate between tumour and normal tissue. Some tumours, such as primary brain-stem gliomas, cannot be visualised without an MRI scanner. MRI scanners also produce sagittal, coronal and axial images, or indeed images in any oblique or double-oblique plane, which allows more accurate determination of tumour volume and precise delineation of the normal tissue at risk [Coffey et al 1984]. The images can also provide

functional information more akin to nuclear medicine and ultrasound [Webb 1988]. However, MRI also has several drawbacks with regard to treatment planning:

- ❖ MR image intensities are not directly convertible to relative electron densities.
- ❖ Artefacts can be introduced by patient motion during the lengthy scanning process.
- ❖ The non-uniformity of the magnetic field and field gradients can also cause geometrical distortion of the images [Lichter et al 1988, Kessler et al 1991].

MRI is a useful tool for providing additional information to the therapy planning process although it is not capable of completely replacing CT scanning. The best approach is to integrate the CT and MRI images, using the CT as the anatomical template. However, correlation of CT and MRI images is indeed a challenging task. The methods by which MRI data can be transferred and integrated into a CT-based planning system have been described by Kessler et al [1991].

1.4 Positron Emission Tomography (PET)

The main reason for the interest in positron emission tomography (PET) is to be found in the nature of the positron decay process. Positrons are positively charged electrons emitted from nuclei that have an excess of protons. Positron emitting radionuclides do not directly emit γ -rays, but when an emitted positron has lost its energy by interaction with the surrounding medium within a short distance of the site of emission, it annihilates by combining with an electron, and two γ -rays with energies of 511 keV each are produced simultaneously. Such a pair of γ -rays produced by annihilation of a positron always travel in opposite directions (180° apart). So, by recording almost simultaneous arrivals in a detector system surrounding the patient, the origin of the emission can be located in three dimensions.

Although PET is not a new concept, having been first proposed in the early 1950s [Wrenn et al, 1951] the clinical indications for positron emission tomography have increased dramatically in the past few years. PET continues to have a major role in patients with neurological, psychiatric and cardiovascular diseases, while the area of most rapid growth during the 1990s has been in oncology. A number of PET radiopharmaceuticals have been utilized for oncological investigations including labelled hormones or their analogues, labelled amino acids, labelled hypoxia agents and labelled thymidine [Hawkins et al 1994,

✓ Shields et al 1995]. The most widely used radiopharmaceutical for oncology at present is flourodeoxyglucose labelled with Fluorine-18 (^{18}F FDG). FDG can be used to:

- (a) facilitate the detection of tumours;
- (b) differentiate between benign and malignant tissue;
- (c) assist in the staging of tumours;
- (d) assess the effectiveness of therapy.

In the case of breast scanning, the PET scanner has a significant advantage over the other imaging techniques. Breast cancer is still the most common lethal malignancy in females. A large number of new or improved techniques have been developed in recent years, yet most patients still require multiple examinations of various organs, including ultrasonograms of the liver, isotope bone scans, mammograms and CT scans. However, PET imaging has recently shown promise as a single technique that might have equivalent or better accuracy than the other current methods combined [Hawkins et al 1994, Shields et al 1995, Wall et al 1991].

Lung cancer is the most common type of cancer world-wide and is usually fatal. In the case of lung cancer, when a solitary pulmonary nodule is seen on a chest x-ray, it must be determined whether it is malignant or benign and the stage of the disease must be established. Often, CT and MRI scans cannot differentiate between the malignant or benign state, and it is necessary to do an histological examination. This involves an invasive procedure such as bronchoscopy, percutaneous biopsy or open-lung biopsy, and it may be necessary for the patient to undergo this procedure more than once during the course of therapy. However, FDG-PET can usually answer the question about the pathology of a solitary nodule and spare the patient the more invasive and expensive procedures.

Colorectal cancer is a common form of malignancy. In this case, PET can give more information over other investigations such as with CT, where it is often difficult to distinguish between a new lesion and a scar. FDG-PET has been used effectively in patients with recurrent colorectal cancer [Strauss et al 1991]. PET can also give valuable information in the case of brain tumours, neurological diseases, and cardiology over the other forms of investigation.

The impact of PET images on the treatment planning process has been assessed by determining the frequency, type, and extent of changes to plans. PET data influenced 34% of the treatment plans examined, and resulted in enlarging portions of the beam aperture up to 15 mm for lung cancer [Munley et al 1999]. Now it is possible to transfer PET images to the treatment planning system, where they are used to mark radiotherapy target volumes [Emri et al 1997, Ackerly et al 2002].

1.5 Use of radiotherapy for coronary artery disease

In addition to the use of radiation to treat malignant disease there has been growth in applications of the treatment of non-malignant disease such as coronary artery disease. Coronary artery disease is one of the most common causes of death in the world. It occurs when the inside walls of the main arteries to the heart have become narrowed by a buildup of fatty material (atheroma). There are several different types of revascularization procedure, which can help to correct this, including coronary artery bypass surgery and coronary angioplasty. The latter leads to less morbidity, is less expensive and has an initial success rate of 90%. According to the British Heart Foundation, nearly 23,500 angioplasties are performed each year in the UK [1999] and in the USA over 400,000 angioplasties are performed over the same period. Approximately 35-50% of these procedures will result in post-angioplasty restenosis [Faxon et al 1994, Weintraub et al 1994, Faxon et al 1995]. Restenosis is the re-narrowing of a blood vessel after angioplasty. Post-angioplasty restenosis is one of the major problems for interventional cardiology today. In recent years, the use of stenting has increased in an attempt to reduce restenosis. In-stent restenosis, however, also affects 25-35% of patients undergoing angioplasty [Fischman et al 1994, Serruys et al 1994]. These rates remain unacceptably high. Recently, several studies have suggested that intravascular brachytherapy has the potential to reduce the rate of restenosis to 10-15% [Condado et al 1997, Teirstein et al 1997, King et al 1998]; however, the final data are not yet available and long-term safety and efficacy have not been established.

Prior to 1994 it was thought that restenosis was caused by proliferation of smooth muscle cells, originating from the medial wall or atherosclerotic lesion, leading to the formation of new intimal mass compromising the lumen [Wilcox et al]. In 1994, studies demonstrated for the first time that restenosis may not be caused by development of an intimal lesion, but rather by abnormal vascular remodelling of the artery in response to balloon overstretch

injury. Vascular remodelling was first described by Glagov et al [1997] in atherosclerotic vessels.

Ionizing radiation has been shown to reduce lesion formation following arterial injury in a variety of animal models [Wiedermann et al 1994a, Waksman et al 1995a, Wiedermann et al 1994b, Waksman et al 1995b, Hehrlein et al 1995, Verin et al 1995], and recent clinical trials have confirmed that this new therapy has the potential to significantly reduce post-angioplasty and in-stent restenosis [Condado et al 1997, Teirstein et al 1997, King et al 1998]. Intravascular brachytherapy drastically reduces neointima formation and vascular remodelling in the porcine coronary artery injury model. Clinically, vascular remodelling after angioplasty has been effectively prevented by intravascular irradiation [King et al 1998]. Intravascular irradiation inhibits the proliferation of adventitial myofibroblasts and the formation of the myofibroblast scar in the adventitia surrounding the injury site.

The different radiation techniques used in the prevention of restenosis can be divided into two broad categories: external and endovascular techniques. In endovascular therapy both temporary implants (catheter-based techniques) and permanent implants (radioactive stents) need to be considered.

Different types of source are used for vascular therapy. For example:

- (1) Point sources (^{32}P), such as stepping sources in modern oncological afterloaders. These are currently only used for peripheral vascular brachytherapy.
- (2) Line sources currently form the dominant source type, as either a chain of seeds (^{192}Ir , $^{90}\text{Sr/Y}$) or a metallic wire (^{90}Y , ^{32}P).
- (3) Volume sources are also in clinical use. These take the form of standard PTCA balloons filled with a solution of ^{188}Re , ^{32}P and ^{186}Re [Dries 1999]. ^{133}Xe has also been studied currently as a potential gaseous-filling medium. Available systems for local delivery of drugs could also be used for the delivery of compounds labelled with radionuclides; studies to determine the use of ^{131}I and $^{99\text{m}}\text{Tc}$ are ongoing. A list of several isotopes, which are used for endovascular brachytherapy and proposed isotopes for use in endovascular brachytherapy are given in Table 1.1. A detailed

description of different types of radiation sources was given by Fox [2002] in a review article.

	Symbol	Applied emission	Half-life	Maximum energy (p>1%)
Clinical	^{192}Ir	γ	74 days	612 keV
	$^{90}\text{Sr/Y}$	β	28.6 years (^{90}Sr)	2.28 MeV (^{90}Y)
	^{90}Y	β	64h	2.28 MeV
	^{32}P	β	14.3 days	1.71 MeV
	^{188}Re	β	17h	2.12 MeV
Preclinical	^{186}Re	β	90.6 h	1.08 MeV
	$^{188}\text{W/Re}$	β	69.4days(^{188}W)	2.12 MeV(^{188}Re)
	^{133}Xe	β	5.25 days	0.35 MeV
	^{131}I	β, γ	8.04 days	0.81 MeV (β) 723 keV (γ)
	$^{99\text{m}}\text{Tc}$	γ	6.02 h	140 keV
Theoretical	^{125}I	X-ray	60 days	35 keV
	^{103}Pd	X-ray	17 days	23 keV
	$^{106}\text{Ru/Rh}$	β	368 days (^{106}Ru)	3.54 MeV
	$^{68}\text{Ge/Ga}$	$\beta+$	288 days (^{68}Ge)	1.90 MeV(^{68}Ga)
	$^{144}\text{Ce/Pr}$	β	284 days (^{144}Ce)	3.00 MeV(^{144}Pr)

Table 1.1 Proposed isotopes for use in endovascular brachytherapy. Most isotopes emit several type of radiation; only the emission which leads to the desired dose in the target tissue is listed [Taken from Dries 1999].

External beam treatments were used for many of the initial animal experiments [e.g. Hehrlein et al 1999]; however there have been no major human trials of the treatment of coronary arteries with this technique. The major disadvantage is that although external beams deliver a very uniform dose to the arterial wall, it is difficult to avoid treating a large volume of heart and tissue beyond it. It is well known that generalised cardiac irradiation can give rise to subsequent coronary artery disease [Stewart et al 1995], so there is reluctance to use a technique which may exacerbate problems in other arteries or in the heart muscle itself. Recently Mosseri et al [1999] have proposed the use of a stereotactic technique using

fluoroscopy to track the position of a stent in the artery. To date, such systems are not commercially available. The potential advantage of external beam irradiation over endovascular approaches include [Croker 1999]:

- (1) No additional catheterisation laboratory time to deliver treatment
- (2) No costs for disposables such as those associated with the new endovascular delivery systems
- (3) The ability to optimise the timing of the treatment in relation to the intervention
- (4) The ability to deliver fractionated therapy that may be associated with fewer late effects
- (5) The delivery of a more homogeneous dose to the vessel wall.

The only gamma emitting isotope currently used is ^{192}Ir [Albiero et al 1998a, Albiero et al 1998b]. This gamma emitter, with a half life of 74 days, has the advantage of deep dose delivery to the target area in the vessel wall, possibly at the junction where the media and adventitia meet. The disadvantage of using ^{192}Ir is the need for additional radiation shielding for catheterisation laboratory personnel and the need for long dwell times of 10-20 min. Overall, clinical experience has shown that ^{192}Ir can be used safely with appropriate precautionary measures and guidelines. Low-energy γ -emitters such as ^{125}I and ^{103}Pd may be easier to use than ^{192}Ir and can deliver approximately the same absorbed doses. The use of other γ isotopes is primarily hindered by the limited ability to concentrate the isotope into seeds small enough to be safely placed into the coronary artery. In addition, ^{192}Ir is comparatively inexpensive.

Radioactive stents have also been used for the prevention of restenosis. Numerous studies of stent implantation have demonstrated a reduction in restenosis compared with angioplasty using balloons and other new devices. The first evaluation of a radioactive stent was reported by Hehrlein et al.[1995]. They implanted a stainless-steel stent (Palmaz-Schatz stents) made radioactive in a nuclear reactor. The stents were highly effective at inhibiting neointimal formation, but might be problematic for permanent implantation as some of the isotopes created have very long half-lives. Consequently, this same group of researchers and others investigated the effects of stents implanted with radioactive phosphorous (^{32}P) [Hehrlein et al 1996, Fischell et al 1994]. This stent was tested in pig coronary arteries at various levels of radioactivity and it was found that both low-activity (0.15-0.5 μCi) and high activity (3.0-

23.0 μCi) stents inhibited neointima formation compared with the control (non-radioactive stents), but those of intermediate activity (1.0 μCi) had nearly twice as much neointima [Carter et al 1996]. The author speculated that either delayed endothelialization or a stochastic effect on extracellular matrix production might be responsible for this puzzling finding.

The rationale for introducing β -emitters to the field of vascular brachytherapy was to provide cardiologists with a safe, easy to use system, which was compatible with the catheterisation laboratory environment, with minimum radiation exposure for both the operator and patient. In addition, the limited penetration of β -emitters has two major advantages: localizing the radiation delivered to the treatment site and minimizing the adverse effect of radiation to the heart.

A variety of β -isotopes, catheter delivery systems and afterloaders are being tested in clinical trials of vascular brachytherapy. Different configurations of β -source are available; among them are wire or seed type solid sources, liquid sources and the radioactive stent. Different types of radiation delivery catheters are available: the non-centered catheter (Novoste, Atlanta, GA, USA) and centred catheter designs either by helical (Guidant, Santa Clara, CA, USA) or segmented balloon (Boston Scientific, Natick, MA, USA) [Waksman 1999]. The afterloaders include a manual hydraulic device (Novoste) and automatic afterloaders (Guidant and Boston Scientific). The liquid-filled balloons use a sealed syringe and the radioactive stent is mounted onto a balloon catheter.

1.6 Detectors for the Verification Treatment Planning

Absorbed dose measurements with conventional dosimeters exhibit limitations when several beams, or dynamic single beams, are combined to form a dose distribution. For conformal therapy, a dosimeter should have the following important features [Farajollahi 1998]:-

- ❖ Reproducibility of response
- ❖ Stability before and after irradiation
- ❖ Independence from dose rate, temperature and radiation quality
- ❖ Linear dose response, so that errors in dose are constant across the dose range ✕✓
- ❖ Simple preparation and analysis
- ❖ Ability to measure 3-D dose distribution with high spatial resolution

❖ Tissue equivalent

Using a water-scanning system together with conventional detectors such as diodes or ionisation chambers, the absorbed dose is measured only at discrete points. The detector response, or signal per unit absorbed dose, may change with the direction of incident radiation for detectors such as diodes. Furthermore, the response of diodes is not completely independent of radiation quality, and corrections may be needed in order to determine the absorbed dose in water. However, all conventional dosimetry methods have their own limitations. Ionization chambers measure absolute dose to a high precision at single points, but their finite size makes resolving areas of high dose gradient problematic. In this case, the construction of an accurate 3D dose distribution is very difficult and time consuming. Improved spatial resolution can be achieved with thermoluminescent dosimeters (TLDs), but measuring a 3D dose distribution is time consuming, because it requires the transfer of the detector from the phantom to a readout device; this extends the measurement time if a sufficiently large number of detectors is used. The TLD, however, has a linear response to absorbed dose over a wide range and its sensitivity is almost energy independent. Film also offers high spatial resolution in a single, two-dimensional plane, and provides excellent relative dose measurements when appropriately calibrated. More complete three-dimensional (3D) dose measurements can be produced by positioning film in multiple planes, although accurate positioning of film in several layers can be a difficult and time-consuming process.

Diamond detectors [Rustgi 1995] and liquid ionisation chambers exhibit an atomic composition closer to that of water, and corrections may not be needed; however these detectors are limited to point dose measurements. Other two-dimensional detectors recently used in clinical applications include Tl (thermoluminescent) sheets [Iwata et al 1995], radio-chromic film [Ertl 1998] and plastic scintillator sheets [Chawla et al 1995]. However, the presence of these non-water-equivalent detectors will cause perturbations in the radiation field and thus affect the dose measurement.

The most recent development in dosimetry has been the use of gel dosimeters. In gel dosimetry, the gel itself forms both a three-dimensional phantom and the detector. Therefore, no corrections are needed to obtain the absorbed dose in a gel phantom using low LET (linear energy transfer) radiations. The gel can be modified to be almost soft tissue equivalent. The

three-dimensional properties of the detector are especially advantageous when used for the verification of treatment planning.

1.7 Gel dosimetry

The objective of radiation therapy is to deliver a high, and usually uniform, dose to the tumour while keeping the dose to the neighbouring healthy tissues as low as possible. However, the tumour and neighbouring healthy tissues bear complex relationships to one another. A clear understanding of the relationships of these structures to one another, as well as the anatomic impact of dose distributions in three dimensions, is essential for designing suitable treatment plans. Improved diagnostic techniques such as CT, MRI, and PET have made it possible to depict anatomical and tumour regions in elaborate detail. The treatment planning CT examination is used to create an electron density matrix [Knöös et al 1986] and further to outline the contour of the patient and to place within it the planning target volume [ICRU Report No. 50, 1993] and organs at risk. Furthermore, for the treatment plan design and evaluation process to be meaningful, the dose at all points of interest must be known throughout the treatment volume with appropriate clinically relevant accuracy. In order to predict dose with adequate accuracy, it may be necessary to take into account point-by-point variation of density and elemental composition of tissues, and to incorporate the three-dimensional nature of radiation transport. Three dimensional dose calculation and display are becoming more accurate, and speed is increasing due to better software design, and faster and more powerful hardware. The beam's eye view display is now available [McShan et al 1980, Goitein et al 1983], and image production and display of patient anatomy in the 3D view is becoming available on commercial machines. To complement this, the three dimensional properties of polymer gel dosimetry hold the promise that three dimensional dose distributions can be measured rapidly and more accurately.

1.7.1 Fricke gel dosimeter

In 1984, Gore et al suggested that aqueous gels containing a Fricke dosimeter solution [Fricke et al 1927, 1966] could be employed to determine radiation dose distribution via MRI. The Fricke gel system, has been considered by a large number of authors [Appleby et al 1988, Olsson et al 1989, Olsson et al 1990, Hazle et al 1991, Schulz et al 1990, Korn et al 1993], and is based on the chemical change of ferrous (Fe (II)) to ferric (Fe (III)) ions, which occurs at low pH as a result of radiation exposure. Both Fe (II) and Fe (III) are paramagnetic contrast agents but they alter NMR relaxation rates to very different extents because of

different electron spin relaxation times [Gore et al 1984a]. The proportion of Fe (II) ions converted to Fe (III), and hence the local value of the longitudinal (T_1) and transverse (T_2) nuclear relaxation times is dependent on the absorbed radiation dose. Thus, a T_1 weighted or T_2 weighted MRI sequence is able to discriminate between regions of space with different absorbed dose [Podgorsak et al 1992]. The ultimate goal has been the use of MRI to determine three-dimensional dose distributions [Olsson et al 1992b, Prasad et al 1991] and the major advantage of MRI ferrous sulphate gel dosimetry is the flexibility to obtain dose distribution in arbitrary planes. Fricke-gel dosimeters also have the favourable radiation dosimetry feature that they are tissue equivalent over a very large photon energy [Kron et al 1993, Chan et al 1993], even at the low energies encountered with Ir-192 [Kron et al 1993]. However one major disadvantage is intrinsic to the Fricke gel medium: ferric ions are able to diffuse quite freely through the gel after irradiation, with a point spread function whose width is about 2mm after 1 hr [Schulz et al 1990]. This leads to a gradual blurring of the radiation dose pattern and a consequent loss of spatial resolution.

1.7.2 Polymer gel dosimeter

The search for a dosimetry technique that allows full 3D imaging of a radiation dose distribution has led to the development of radiation-sensitive gels. Developments in gel dosimetry have recently been reported by McJury et al [2000] indicating that Day and Stein first investigated gels containing Folin's phenol, which changed colour upon irradiation in 1950. Viscosity measurements [Alexander et al 1954, Boni 1961] and changes in spectrophotometric measurements [Andrews et al 1957] were all found to correlate with the absorbed radiation dose. McJury et al [2000] also reported that measurements of photon and electron depth doses were made by Andrews et al [1957] using agar gel. In 1958, Hoecker and Watkins reported that radiation induced polymerisation may be useful as a dosimeter. Radiation-induced polymerisation was also used at an early stage in chemical dosimetry [Swallow 1973] as radicals arising from the water radiolysis were known to initiate polymerisation in a monomer solution; this was as reported by Stephen in 1991.

In 1993, Maryanski and co-workers introduced a new dosimeter consisting of N, N'-methylene-bisacrylamide (bis), acrylamide, nitrous oxide, agarose, (BANANA) based on radiation induced polymerisation. Here, acrylic molecules placed within an agarose gel matrix polymerised after irradiation, with the degree of polymerisation being strongly related to the absorbed dose received by the gel. Since 1993, many groups have investigated

polyacrylamide gels (PAG) and their chemical composition has been optimised; for example agarose has been replaced by gelatin (BANG gel) [Maryanski et al 1993], and acrylamide has been replaced by acrylic acid (BANG2 gel) [Maryanski et al 1994].

The polymer gel dosimeter utilizes the mechanism of radiation induced polymerisation of the monomer [Hoecher et al 1958]. The NMR spin-spin relaxation rate ($R_2=1/T_2$) of BANG type gels shows a linear dose response up to 12 Gy. The dose sensitivity ($\sim 0.34 \text{ s}^{-1}\text{Gy}^{-1}$) is substantially higher than that of the Fricke gel and is stable with time [Maryanski et al 1994, 1996]. When the gel is irradiated, free radicals released during the radiolysis of the water initiate polymerisation and cross-linking of the monomers, with polymer concentration being proportional to absorbed dose. Oxygen is a well known free radical scavenger [Maryanski et al 1997] and will reduce the sensitivity of the dosimeter if present in dissolved form [Maryanski et al 1994, Maryanski et al 1997]. Oxygen must, therefore, be removed from the gel during manufacture and the gel phantom should be firmly sealed to prevent ingress of air. After irradiation, the dosimeter is analysed or imaged. A number of techniques can be employed to analyse spatially the degree of polymerisation within the irradiated gels. After the radiation induced polymerisation of co-monomers in a gel matrix, the NMR parameter T_2 (the transverse relaxation of the water protons in the system) is mapped using MRI. Optical tomographic techniques have also been explored [Gore et al 1996, Maryanski et al 1996] in order to exploit the simultaneous changes in optical density of the polymer gel post irradiation. More recently, Fourier Transformation (FT) Raman spectroscopy has been used [Baldock et al 1998]. FT Raman spectroscopy affords direct measurement of the composition of the medium and when applied to polyacrylamide gels, allows the investigation of the changes in gel composition following irradiation. Baldock et al [1998] indicated that Raman imaging could also be applied to gels irradiated with a variable dose distribution to yield high-resolution dose maps.

Current polymer gel dosimetry offers a number of advantages over other dosimetry methods, mainly:

- ❖ Potential for multi-planar, 3D dose distributions with high spatial resolution of the order of $\leq 0.2 \text{ mm}$ in plane for MRI [Häfeli et al 2000, Ertl et al 2000, Amin et al 2001, Berg et al 2001] and better than 1 mm^3 for optical scanning [Doran et al 2001, Oldham et al 2001].

- ❖ Dose sensitivity is independent of both dose rate and radiation energy for low LET radiations [Maryanski et al 1996].
- ❖ The gel itself a dosimeter, thus there is no disturbance of the dose distribution by additional measuring devices, and the gel is of muscle tissue equivalent composition and density [Maryanski et al 1996].

In addition, the gel can take up any shape, inhomogeneities can be placed within the phantom, and gel dosimeters do not suffer from the problems of ion diffusion associated with Fricke gel dosimeters [Schulz et al 1990, Olssen et al 1992].

On the other hand, PAG type gels still have several drawbacks such as:

- ❖ Difficulty of manufacture (requiring hypoxic conditions during their manufacture).
- ❖ PAG type gel is oxygen sensitive, and even a trace amount of oxygen can lead to a complete failure of the polymerisation reaction.
- ❖ PAG gel contains a neurotoxin acrylamide, and repeated skin contact, inhalation, or swallowing of this constituent may cause nervous system disorders.
- ❖ As a phantom vessel wall material only glass and Barex™ are useable [Maryanski et al 1994, Bonnett et al 1999].

1.8 Aims of the thesis

Overall aim brief of this thesis was to investigate polymer gel dosimetry, a relatively new three-dimensional dosimetric technique.

The detailed aims were to:

- ❖ Improve the current manufacturing technique for gel dosimetry used at Leicester.
- ❖ Investigate the accuracy of absorbed dose measurements.
- ❖ Investigate the use of gel dosimetry for electron and orthovoltage measurements.
- ❖ Investigate the use of high resolution MRI and PAG in the dosimetry of β sources for endovascular brachytherapy.
- ❖ Implement gel dosimetry for combined treatments using photons and electrons.
- ❖ Modify the tissue equivalent gel so that it is bone equivalent.
- ❖ Investigate the manufacturing technique and different characteristics of normoxic MAGIC gels.

Chapter 2

Review of previous work

2.1 General properties of radiotherapy gel dosimeters

Over the last 16 years, there has been a continuous development of gel dosimetry. In 1984, Gore and co-workers proposed a method of using the well-known Fricke dosimeter [Fricke et al 1927] together with a gelling substance in order to achieve true three dimensional dosimetry using MRI. The method was based on the radiation-induced conversion of ferrous ions (Fe^{2+}) to ferric ions (Fe^{3+}) in a gel, and will hereafter be referred to as FeGel. This innovation encouraged a number of groups to take part in the development of a new dosimeter, the polymer gel dosimeter. The development of this dosimeter will be reviewed in chronological order.

In 1993, Maryanski et al introduced a new type of tissue-equivalent dosimeter, as an alternative to the Fricke gel dosimeter based on radiation induced polymerisation. They used agarose as a gelling agent, and Acrylamide and N,N'-methylene-bis acrylamide as comonomers. They created the acronym BANANA to describe the gel, standing for Bis, Acrylamide, Nitrous oxide And Agarose. In this work, they demonstrated the feasibility of using radiation-induced polymerisation and cross-linking in an aqueous gel to record radiation doses and dose distributions by measuring changes in proton NMR relaxation rates. They also demonstrated that the BANANA gel has some distinct advantages over other approaches to measuring dose distributions, such as the lack of post irradiation diffusion blurring, which is a problem with Fricke-dosimeter based gels.

In 1994, Maryanski et al developed a new formulation of the tissue-equivalent polymer-gel dosimeter. This new gel was referred to as BANG (Bis, Acrylamide, Nitrogen and Gelatin). BANG gel was composed of aqueous gelatin infused with acrylamide and N,N'-methylene-bis acrylamide monomers, and made hypoxic by nitrogen saturation. They showed that the irradiation of the gel caused localized polymerisation of the monomers, which, in turn, reduced the transverse relaxation times of water protons. They showed that the dose dependence of the NMR transverse relaxation rate, R_2 , was reproducible and was linear up to 8 Gy with a slope of $0.25 \text{ s}^{-1} \text{ Gy}^{-1}$. They also showed that the radiation-induced polymers do not diffuse through the gel matrix, and that the dose distribution recorded by BANG gels are stable for long periods of time. The distributions are visible and their optical densities are

dependent on dose. They observed that the temperature at the time of irradiation does not appear to affect the dose response, but the temperature at the time of imaging has a significant effect. They also reported that the advantage of BANG gel over BANANA is its lower R_2 value. Another advantage of BANG gel is that it is more transparent than BANANA gel.

The 37th annual meeting of American Association of Physicists in Medicine was held in Boston, USA on 23-27 July 1995. At this meeting, five scientific papers on polymer gel dosimetry were presented. Maryanski et al [1995a] reported that the dose sensitivity (slope of the linear portion of an R_2 -dose response), the maximum relaxation rate at which the dose response saturates, and the saturation dose, were all found to depend strongly on the cross-linker fraction. At the same time, Maryanski et al [1995b] reported that the dose sensitivity decreased with increasing temperature at the time of scanning. They measured dose sensitivity to be $0.52 \text{ s}^{-1}\text{Gy}^{-1}$ at 5°C reducing to $0.15 \text{ s}^{-1}\text{Gy}^{-1}$ at 40°C , thus decreasing by more than $0.01 \text{ s}^{-1}\text{Gy}^{-1}$ per degree centigrade. Audet et al [1995] reported that an increase in the gelatin concentration from 4% to 6% decreases the dose sensitivity from 0.45 to $0.34 \text{ s}^{-1}\text{Gy}^{-1}$, but has little effect on the R_2 -dynamic range ($\sim 4 \text{ s}^{-1}$) and dose range ($\sim 10 \text{ Gy}$). They also reported that the dose response was independent of purging oxygen from the gel. Wong et al [1995] compared the radiation dose distributions produced by photons and electrons using the FAX (Ferrous-Agarose-Xylenol orange) and BANG gel dosimeters. They also compared the result of the BANG-MRI method with a computerised treatment planning system (GE Target-2) and reported that the radiation induced polymerisation in a polymer gel dosimeter provides a rapid qualitative evaluation of three dimensional dose patterns post-irradiation. It also provided adequate accuracy, stability and reproducibility to be used for quantitative testing of radiation dose distributions with delays between irradiation and measurement of up to several months. Ibbott et al [1995] described the use of BANG polymer gel for QA procedures with linear accelerators, an HDR remote afterloader, and Gamma Knife radiosurgery.

The dependence of dose sensitivity on both the monomer and cross-linker concentration was investigated by Baldock et al [1996]. They reported that doubling both monomer and cross-linker concentrations from 3% to 6% gave an increased sensitivity from $0.28 \text{ s}^{-1}\text{Gy}^{-1}$ to $0.56 \text{ s}^{-1}\text{Gy}^{-1}$. The result indicated a linear relationship of transverse relaxation rate (R_2) with dose up to at least 6 Gy, with saturation occurring in the region of 20 Gy. Three dimensional

isodose plots for 40 kV x-rays using a polymer gel dosimeter was investigated by Baldock et al [1996b]. These plots were in good agreement with measurements made with radiochromic film. To investigate dose distributions in external beam breast therapy, Baldock et al [1996c] designed a phantom that was constructed using 3mm thick Barex sheets. The phantom was filled with BANG gel and irradiated with 6 MV photons and, finally three dimensional isodose plots were drawn using the MRI images. These compared well with plots generated on the treatment planning system. Audet et al [1996] investigated the use of polymer gel MRI dosimetry as a verification tool for 3D conformal radiotherapy.

In 1997, the effects of varying the weight fraction of the crosslinker N,N'-methylene-bisacrylamide per total amount of monomer, and the temperature at the time of NMR measurement, on the dose response of a BANG polymer gel dosimeters were investigated by Maryanski et al [1997]. Their results indicated that the dose sensitivity (slope of the linear portion of an R_2 -dose response) and the maximum rate at which the R_2 -dose response saturated ($R_2^{\max}$) depended strongly on the crosslinker fraction and on the temperature at the time of the R_2 measurement.

Baldock et al in 1998a calculated the sensitivity of different batches of PAG gel. They reported that the sensitivity for five different batches of PAG in the range up to 10 Gy was $0.0285 \text{ s}^{-1} \text{ Gy}^{-1}$ for the mean spin-lattice relaxation rate (R_1), with a standard deviation of 1.25%. The overall reproducibility between batches was calculated to be 2.69%. A new method of calibrating gel dosimeters was reported by Oldham et al in 1998. Two test tubes of 2.5mm diameter and 20mm length were irradiated separately with a $10 \times 10 \text{ cm}^2$ field end-on in a water bath, and characteristic depth dose curves were drawn. A calibration was then determined by fitting the depth-dose measured in water, against the measured change in relaxivity with depth in the gel. They also compared their new calibration data with the standard method, where five identical test-tubes of gel were irradiated to different known doses between 2 and 10 Gy. Their result indicated that the percentage uncertainties in the slope and intercept of the calibration fit were lower with the new method by factors of about 4 and 10 respectively. In the same year, De Deene et al [1998] investigated the applicability of BANG gel for the verification of conformal radiotherapy treatment plans and reported that in the case of standard beams, the gel dosimeter corresponded quantitatively well with results using diamond detectors. They also reported that the slope of the dose response curve decreases $6.3 \times 10^{-3} \text{ s}^{-1} \text{ Gy}^{-1}$ with each increase of one degree Celsius at the time of scanning.

The water equivalence of Fricke and PAG gel in terms of radiological properties was studied by Keall et al [1999]. They investigated the macroscopic photon and electron cross-section parameters. Their results indicated that for 6 MV photons, the gel depth dose curves exhibited <1% difference between the water depth dose curves and for 6 MV electron beam depth dose curves were all within 1 mm of those in water. They also found the gel to be almost water equivalent.

McJury et al [1999a] reported an investigation of polymerisation kinetics in PAG dosimeters and the effect of oxygen diffusing into the dosimeter. They found that, post-manufacture, irradiated and unirradiated gels show a continuous change in R_2 . In unirradiated gels, the change in relaxivity can be attributed to the initiation of polymerisation by the presence of free radical impurities in the gel components. They suggested that imaging should be performed at a minimum of three to four days post-irradiation to achieve a good percentage of the maximum attainable sensitivity of the dosimeter.

In 1999 Hepworth et al investigated the diffusion of oxygen and the effect of increasing concentrations of oxygen in the PAG. They calculated the diffusion coefficient to be $(8 \pm 2) \times 10^{-6} \text{ cm}^2 \text{ s}^{-1}$ under the assumption that the diffusion is concentration independent. They also used this method to measure a quantitative relation between oxygen concentration and its inhibitory effect on gel polymerisation. They showed that very low levels of oxygen contamination (0.05-0.3%) can have an inhibiting effect upon the PAG. In the same year Hepworth et al [1999a] introduced bone-like inhomogeneities into the gel and successfully measured the dose distribution around these inhomogeneities.

Baldock et al [1999a] calculated the uncertainty in polymer gel dosimetry. They found that the uncertainty was about 3% at 8 Gy and 7% at 2 Gy. They also reported that the most significant reductions in overall uncertainty will be achieved by reducing the noise in the R_2 measurement.

A new type of polymer gel, the N-vinylpyrrolidone argon (VIPAR) gel, was developed and investigated as an MRI dosimeter by Pappas et al in 1999. The gel composition was 4% w/w of N-vinylpyrrolidone, 4% w/w of N,N'-methylene-bis acrylamide, 5% w/w of gelatine type A and 87% w/w of water. For this gel there was a linear relationship between absorbed dose and R_2 , and the dose sensitivity was $\sim 0.1 \text{ s}^{-1} \text{ Gy}^{-1}$.

Bonnett et al [1999] investigated the wall effects of four radiotherapy phantom materials (glass, Barex™, Perspex and PVC) on a polymer gel. Their result indicated that the inhibition of polymerisation near the phantom wall is particularly evident for PVC and Perspex. They also showed that for PVC and Perspex this effect increases with time after manufacture when the phantoms are left in an oxygen atmosphere and the effect is less pronounced with a higher absorbed dose. They suggested that Barex™ is the best material for making a phantom for polymer gel dosimetry, because Barex™ itself is a tissue equivalent, it is possible to mould it to any shape, and it has barrier properties almost as good as glass. Rousselle et al [1999] demonstrated that gels containing no co-monomer such as Fricke can be considered as water equivalent and gels containing co-monomers such as BANG-2 are brain equivalent. From this point of view, they also demonstrated that they are all convenient for use in radiosurgery simulation, since dose planning is actually based on narrow beam dose measurements in water.

Kaurin et al [1999] verified both treatment simulation and the three-dimensional dose distribution for a four-field oblique and a lateral flying wedge pelvic plan using a novel anthropomorphic pelvic phantom and a tumour vessel filled with polymer gel. They found an absolute three-dimensional dose distribution error of about 6%, with agreement between measured and calculated isodose lines of less than ± 2 millimetres. Their results suggested that polymer gel dosimeters together with ionisation chamber measurements can be used with anthropomorphic phantoms to quantify treatment set-up accuracy and verify relative and absolute three dimensional dose distributions in any plane.

In 2000, more than 17 papers were published on polymer gel dosimetry. Baustert et al [2000] described an optimisation strategy used to identify accurate and practical methods of measuring the T_2 values in gel dosimeters. They also described MR imaging techniques to measure T_2 values and the choice of image acquisition parameters. They compared four sequences: spin echo (SE), Multiple spin echo (MSE), fast spin echo (FSE) and echo planar spin echo (EPI), and the results were analysed in terms of accuracy, signal-to-noise ratio and acquisition time. The MSE sequence yielded results with better accuracy than the other sequences. They also suggested that when speed is required, the FSE sequence might be used, if a reduction in accuracy of 0.7% compared with the MSE sequence is acceptable.

De Deene et al [2000a] investigated the temporal stability of polymer gel. They described two types of instability: one affects the slope of the dose- R_2 plot and the other affects the intercept of the dose- R_2 plot. They observed that the first kind of instability lasts only 12 hours after irradiation and the second kind lasts for up to 30 days, and is related to the gelation process of gelatin. It was also shown in their experiment that the heating history during the manufacture of the gel affects the absolute R_2 value of the gel. The same year Murphy et al [2000a] studied a new formulation of polymer gel where the less toxic monomer sodium methacrylate was used instead of acrylamide. They reported that without changing the pH, the R_2 -dose sensitivity was half that of BANGTM gel. They also reported that the background R_2 and dose sensitivity depend on pH. Proton spectroscopy was applied by them to study the gels and it was reported that the crosslinking co-monomer was consumed more readily than the monomer.

Cosgrave

Cosgrave et al [2000] verified treatments plans using PAG gel for a three-field coplanar arrangement, using linac jaws for field shaping, and a four-field, conformal, non-coplanar plan using precision-cast lead alloy shielding blocks. Their result indicated that relative dose distributions were reproducible and compared favourably with calculations. They also showed that the standard deviations on the mean area enclosed by the $\geq 50\%$ isodose lines measured in three orthogonal planes were 6.4% and 4.1% for the coplanar and non-coplanar plans respectively. Their measured distributions were also consistent with planned distributions, with isodose lines agreeing to within a few millimetres. However their measured absorbed doses were on average 23.5% higher than the planned distribution. They also reported that this differences might be due to the temperature differences in the gel during imaging, oxygen concentration of the gels, gel pH, inhomogeneous field distributions in the imaging coil, difference in the size of the calibration vials and phantoms.

In 2000[b,c] De Deene et al published another two papers. In one, they reported an analysis of the eddy currents as they appear in the multiple spin-echo sequence. They also reported a compensation method for eddy current effects in multi-echo T_2 mapping. In another study they shown experimentally that the slice profiles of transverse base images recorded by use of a multiple spin echo sequence vary with slice position due to B_1 field inhomogeneities in the head coil. Additionally, they demonstrated that R_2 maps obtained by a multiple spin-echo sequence depend quantitatively on the slice position. In this study they suggested that when scanning a gel phantom, the regions of higher B_1 field uniformity should be exploited, or the

body coil should be used instead of the head coil. They also suggested a combination of a receive-only surface coil and the body coil as transmitter may offer an interesting alternative. Recently, De Deene et al [2000d] also published one more paper where they investigated MR-based polymer gel dosimetry as a three-dimensional dosimetry technique in conformal therapy. The dose maps were measured using polymer gel and compared with the dose distribution measured using radiographic film and showed that the average root-mean square structural deviation between the dose maps obtained by gel and film dosimetry amounted to less than 3%.

Haraldsson et al [2000] described a safe mixing procedure for the toxic ingredients used for polymer gel dosimeters. They obtained a dose response that is linear and reproducible from 0-8 Gy with a sensitivity of $0.211 \text{ s}^{-1}\text{Gy}^{-1}$. They drew depth dose curves for photons and electrons, and compared the result with diode data; they found a deviation of less than 3% between two methods. They also investigated Barex as a phantom material and found it to be favourable compared with glass.

Different methods are used for calibrating polyacrylamide gel (PAG) dosimeters. Most of the methods involve nitrogen filled glass vials containing polymer gel. The glass vial is then irradiated using ionising radiation. In one study, Michael [2000] et al performed Monte Carlo simulations to examine the effects on the radiation field due to the glass vial and the lack of backscatter material due to the nitrogen filled space. Their result indicated that the influence of the glass and the nitrogen filled space are negligible.

The extent of the linear dose response and the dynamic dose range of VIPAR (*N*-vinylpyrrolidone argon) gels were investigated by Kipouros et al [2001]. They reported a satisfactory agreement between the calibration results driven using 6 MV x-rays and the ^{192}Ir sources and implied that the response of the VIPAR gels is independent of photon energy and dose rate. They also reported that the gels exhibit a linear dose response up to 40 Gy.

Energy and dose rate dependence of BANGTM-2 polymer gel was studied by Novotny et al [2001], who reported that the BANGTM-2 gel dosimeter sensitivity decreased with increasing photon and electron energy. They also observed no trend in polymer gel dosimeter sensitivity with dose rate for both photon and electron beams. In another study, the same group

[Spevacek et al 2001] also studied temperature dependence of polymer gel dosimeters and reported that R_2 decreased with increasing temperature with an exponential behaviour.

Three different calibration methods were compared by Cardenas et al [2002]. These were: off-site manufacturer provided calibration curve; on-site external tube gel calibration; and on-site internal normalised gel calibration protocols. Their results showed that large variations were observed between theoretical dose distributions with the distributions generated using manufacturer calibration and on-site calibration data. On the other hand, good agreement was observed between theoretical dose distributions and the distributions generated using on-site internal normalised gel calibration protocols. In conclusion they suggested that an independent on-site internal normalised gel calibration must be performed for each batch of gel dosimeters in order to account for the variations in dose sensitivity caused by various uncontrollable conditions in a clinical setting, such as oxygen contamination, temperature changes and shelf life of the gel between manufacture and MR acquisitions.

In 2002 Salomons et al [2002] reported that temperature changes, proportional to the absorbed dose, were observed in the irradiated gels, reaching a maximum of 12 °C under high dose conditions, depending on the thermal boundary conditions. This has several practical implications, for example, using small vials of PAG to calibrate large phantoms may not be appropriate since temperature differences during irradiation between the calibration vials and phantom may alter the morphology and quantity of the polymer formed, even when irradiated to the same dose.

De Deene and Baldock [2002c] provided an optimised protocol to acquire a set of dose maps within the shortest time possible for a required dose resolution. In that study they showed that a multi spin-echo sequence is preferable to a single spin-echo sequence, and that it is advantageous to make the echo time spacing as short as possible. However, in another study Baldock et al [2001] demonstrated that the echo spacing time 50 ms is more appropriate compared to 20 ms. The dose range and response reported by several authors are listed in Table 2.1.

Reference	Type of gel	Dose range (Gy)	Dose response ($s^{-1}Gy^{-1}$)
Maryanski et al [1994]	BANG-1	8	0.25
Maryanski et al [1996]	BANG-2	12	0.34
Maryanski et al [1998]	BANG-3	2.3	4
Baldock et al [1996]	BANG-1	6	0.28
Oldham et al [1998b]	BANG-1	7	0.233
De Deene et al [1998]	BANG-1	10	-----
Farajollahi et al [1999]	BANG-1	10	0.28

Table 2.1 comparing the dose range and response reported by several authors for different formulations of BANG™ gel.

2.2 Applications: brachytherapy, stereotactic radiosurgery, and IMRT

The potential use of polymer gel dosimetry to measure complex dose distributions such as in brachytherapy, stereotactic radiosurgery, IMRT has been studied during last few years by several groups. A few important papers are reviewed below:

In 1996, Maryanski et al introduced another type of polymer gel called BANG-2, containing 3% N,N'-methylene-bis acrylamide, 3% acrylic acid, 1% sodium hydroxide, 5% gelatin, and 88% water, where all percentages are measured by weight. This was claimed to be an improved formulation of the polymer gel and differs from BANG mainly in the substitution of acrylic acid for acrylamide. They reported that BANG-2 has a linear response that is independent in energy and dose rate. They used this gel for calculating dose distribution in stereotactic radiosurgery and HDR brachytherapy and they showed that there is excellent agreement between the dose distributions predicted using treatment planning calculations and those measured using the gel method. The utility of the BANG polymer gel dosimeter for evaluating repeat-fixation stereotactic radiation therapy was investigated by Ibbott et al [1996].

Dose distributions around beta-emitting rhenium sources (Re-188/186) used for vascular brachytherapy were studied by Maryanski et al [1997b] using BANG polymer gel. They used a 4.7 T MRI machine and 25 mm diameter birdcage coil for imaging purposes, and obtained a spatial resolution of approximately 120 micrometers. Ir-192 HDR source was characterized using BANG gel by Martin et al [1997]. They also compared BANG polymer gel data with TLD and Radiochromic film data, and there was good agreement between them.

The dose distribution for parallel opposed irradiation and a more complex nine field static tomotherapy intensity modulated irradiation were studied by Oldham et al [1998a]. There was good agreement between the component-delivery dose algorithm and the Peacock planning-system dose algorithm. They also reported that the spatial uniformity of gel sensitivity to radiation was dependent on the percentage of oxygen, which must be eliminated for the gel dosimeter to be of use.

Farajollahi et al [1999] investigated the properties of the BANG polymer gel and its use in the dosimetry of low dose rate brachytherapy. Their result indicated that the response of the gel was reproducible and linear up to 10 Gy. They also reported that the gel was tissue equivalent and response is independent of energy. The slope of the calibration curve increased from $0.28 \pm 0.01 \text{ s}^{-1} \text{ Gy}^{-1}$ to $0.50 \pm 0.02 \text{ s}^{-1} \text{ Gy}^{-1}$ for an increase in monomer concentration from 6 to 9%. They also measured the absorbed dose distribution for a straight applicator containing 36 ^{137}Cs sources and compared these results with both results measured with thermoluminescent dosimeters (TLDs) and calculated values, with good agreement being found. McJury and co-workers [1999b] investigated the dosimetry of a clinical ^{192}Ir source using a polyacrylamide gel (PAG) dosimeter. They compared experimental measurement of dose versus radial distance from the centre of the source with calculations produced with a Nucletron NPS planning system and found good agreement between the planning system and gel measurements. The mean difference between measured dose and calculated dose was 0.17 Gy with a SD of 0.13 Gy. Ibbott et al [1999] characterized a new brachytherapy source by polymer gel dosimetry. Their result indicated that the polymer gel dosimeter is a valuable device for characterizing brachytherapy sources. Gluckman et al [1999] verified 3D-conformal and IMRT treatment planning using a polymer gel, and the calculated and measured isodose surfaces agreed to within 2 mm, and in the low dose regions the differences were under 5%. The measured maximum dose was slightly lower than the predicted dose.

A high resolution dose profile from Leksell Gamma Knife was produced by Ertl et al [2000] using BANGTM polymer gel with a 3 T whole body scanner. They obtained excellent agreement when the gel data were compared to film dosimetry and calculated data. They also reported an in-plane resolution of 0.195 mm. Wu et al [2000] presented measurements of 3-D dose distributions around balloons filled with Re-188 used for the treatment of neointimal hyperplasia. They used BANG gel dosimeters that were modified for linear response up to 30

Gy. They suggested that polymer gel dosimeters could be used to measure the 3-D dose distribution around a radioactive coronary balloon dilatation catheter.

When using MRI for evaluating the response of polymer gel dosimeters, it is important to evaluate the pulse sequence used for determining T_2 . A multiple-spin-echo sequence is available on every clinical MRI scanner, but Baldock et al [2001] indicated that the sequences are not usually optimised for determining the range of transverse relaxation times, that are encountered in polymer gel dosimetry. They suggested that the echo spacing is a parameter of particular significance, and this should be selected to ensure that the uncertainty in T_2 is minimised.

A VIPAR polymer gel dosimeter was used to measure profiles of 6 MV x-ray stereotactic beams of diameter 5 and 10 mm by Pappas et al [2001]. They compared their results with the measurements of radiographic film and a PinPoint ion chamber and showed that the VIPAR gel-MRI method can result in improved resolution of the penumbra region and it can also quite accurately provide relative depth dose data. They also reported that the VIPAR gels have a lower dose sensitivity than the BANG gels, but that they exhibit a linear dose response up to 32 Gy. VIPAR gels were also utilised for intravascular brachytherapy by Papagiannis et al [2001] who reported that their experimental results were in good agreement with Monte Carlo calculations.

High dose variations across small spatial distances, as found in brachytherapeutic applications or radiosurgery and especially γ -knife therapy, are difficult to quantify by standard dosimetry. Berg et al [2001] reported that using gel dosimetry based on high resolution MRI, it is possible to quantify dose distributions characterized by steep dose gradients. In their study they used a 3 T MRI scanner and achieved in-plane resolution of <0.2 mm. They also investigated the sensitivity of the longitudinal relaxation rate R_1 and transverse relaxation rate R_2 and reported that the highest sensitivity was achieved by T_2 imaging and that T_1 may be useful for dose imaging at high spatial resolution.

In 2001 De Deene et al investigated the applicability of MR-based polymer gel dosimetry to the measurement of absorbed dose distributions at short distances from iridium-192 brachytherapy point sources. In this paper, they also discussed different methodological problems that may result in significant errors in the measured dose distribution, such as

physico-chemical mechanisms, oxygen permeability of the catheter material, and monomer-diffusion-related effects during irradiation.

Image distortion in MRI-based polymer gel dosimetry of Gamma Knife stereotactic radiosurgery systems was studied by Watanabe et al [2002]. Image artefacts were studied by varying the direction of frequency encoding and the receiver bandwidth. They reported that the measured dose distributions were shifted 1.8 ± 0.5 mm in the frequency encoding direction and the magnitude of the shift was inversely proportional to the receiver bandwidth. They also used a CT scanner, and comparison of MRI with CT showed the same image shift. In conclusion they reported that the discrepancy was caused by MR image distortion due to a difference in susceptibility effects between the phantom and the fiducial markers of the Leksell localization box.

2.3 Gel measurement using optical CT, x-ray CT and ultrasound

For polymer gel dosimetry, the main imaging modality of choice to date has been MRI. There are alternative methods currently under investigation such as optical CT, x-ray CT and ultrasound. A few investigations based on optical CT, x-ray CT and ultrasound are reviewed below:

✓ In 1996, an optical system for measuring dose distributions in polymer gel was developed by Gore et al [1996]. This measured three-dimensional dose distributions by scanning the polymer gel with a laser beam, as reported by Maryanski et al [1996, 1996b]. The dose response mechanism relies on the production of light-scattering polymer micro-particles, which result from the polymerisation of acrylic comonomers dispersed in the gel. The scattering produces an attenuation of transmitted light intensity that is directly related to the dose and independent of dose rate. For BANG polymer gels, the shape of the dose response curve depends on the fraction of the cross-linking monomer in the initial mixture and on the laser light wavelength. The optical tomographic technique is based on the same principles that govern x-ray computed tomography. Dose distributions are reconstructed from changes in optical density of the irradiated polymer gel over a series of projections taken from different angles. The results have proved the ability of polymer gels to provide an optical recording medium for radiotherapy dosimetry. A reconstruction method using optical CT for gel dosimetry was described by Kelly et al [1996]. ✓

Maryanski [2000a] et al investigated the relative merits of optical CT vs. MRI scanning of BANG gels which were irradiated with ^{125}I seeds used for prostate brachytherapy implants. They also measured an anisotropy function, radial dose function and dose rate constant from the dose maps generated by gel scan data and compared this data with TLD data obtained using solid water and Monte Carlo calculations. Their result indicated that the accuracy of relative dose measurements using both scanning methods was better than 3.5%, while the dose calibration error was within 5%. Maryanski et al [2000b] studied the effect of the catheter on near-field dose distributions reconstructed from optical laser CT scans of BANG polymer gels irradiated with beta sources.

In 2001 Oldham et al [2001] showed that gel dosimetry in conjunction with optical-CT scanning can yield dose maps that were of sufficient accuracy, resolution (1 mm^3), and precision to allow verification of complex radiosurgery deliveries. They also used an MRI scanner and reported that the MR gel-dose maps were found to have poorer precision than optical-CT dose map.

An optical computed tomography scanner (OCT) based on a broad beam light source and a two-dimensional charge-coupled device detector was developed by Doran et al [2001b]. In this paper they reported equipment specifications and discussed problems and solutions. They also reported preliminary results using Fricke gel with the resolution of $0.14 \times 0.56 \times 0.56\text{ mm}^3$. In conclusion, they reported that OCT is less expensive than MRI scanner and it could be used for the measurement of gels used in dosimetry.

✓ Hilts et al [2000] proposed a new three-dimensional dosimetry technique using x-ray computed tomography to analyse polymer gels. The technique involves analysing a well-known polymer gel dosimeter with x-ray CT instead of MRI or optical CT. They developed a CT imaging protocol to optimise CT images of PAG. They also investigated the reproducibility of the dose response and the use of CT to analyse PAG is compared with MRI. Their result indicated that the low dose resolution is the limiting factor of the CT PAG dosimetry technique but in a high dose gradient it can accurately localize the dose distribution.

Changes in the linear attenuation coefficient of polymer gel dosimeters post-irradiation enable the imaging of dose distributions by x-ray computed tomography. Trapp et al [2001] ✓

investigated various compositions of polymer gel dosimeters manufactured from acrylamide, bis acrylamide and gelatin or agarose using CT. They reported that increasing the monomer concentration increases the CT-dose sensitivity of the gel dosimeter and dose sensitivity further increases by replacing gelatin with agarose. They also reported that dose resolution was optimal for gel dosimeters composed of 5% gelatin, 3% acrylamide, 3% bis-acrylamide and 89% water.

Post irradiation changes in the linear attenuation coefficient, μ of polymer gel dosimeters, were measured by Trapp et al [2002] using x-ray CT. They showed that the post irradiation change in μ is proportional to the change in density of the gel, and that the density of fully polymerised area was increased by approximately 1%. The density increase in an irradiated polymer gel dosimeter is related to the volume decrease and the volume decrease implies that there will be some spatial change within the gel.

Mather et al [2002] reported a new method for evaluation of 3-D radiotherapy polymer gel dosimeters using ultrasound to assess the significant structural changes that occur following irradiation. The ultrasound parameters of acoustic speed of propagation, attenuation and transmitted signal intensity were measured as a function of absorbed radiation dose. They reported that all parameters displayed a strong variation with absorbed dose that continued beyond an absorbed dose of 15 Gy. They concluded that ultrasound shows great potential as a technique for the evaluation of polymer gel dosimeters.

2.4 Gel measurement using spectroscopy

The chemical changes at the molecular level of polymer gel before and after irradiation can be studied by several techniques. For example, NMR spectroscopy and FT-Raman spectroscopy have the potential to provide quantitative information on the presence of different chemical groups in a molecule. Several groups have used these methods to study polymer gels. A few of them are reviewed below:

Fourier transform (FT) Raman spectroscopy studies were undertaken to investigate cross-linking changes during the copolymerisation of polyacrylamide gels by Baldock et al [1998b]. Their results demonstrated the potential of FT-Raman spectroscopy for ionising radiation dosimetry using polyacrylamide gels.

Murphy et al [2000] evaluated proton spectroscopy as a method for quantifying radiation induced changes in polyacrylamide gel dosimeters. They showed that MR methods of directly measuring the levels of monomers in polyacrylamide gels can be used to calculate absolute dose more directly than relaxation time images. They imaged a large gel phantom with an echo-filter technique to map the distribution of monomers directly, and then the image was normalized to the water signal and converted into an absolute dose map. There was good agreement between their measured dose and planned dose. They also plotted calibration curve for acrylic protons belonging to acrylamide and bis-acrylamide vs. absorbed dose. The dose response was approximately linear within the range 0-7 Gy.

In 2001 Lepage et al [2001a] characterised the chemical changes occurring in a PAG radiation dosimeter using ^{13}C -NMR, ^1H -NMR, and FT-Raman spectroscopy. They showed that irradiation of acrylamide and bis-acrylamide in a gelatin matrix leads to copolymerisation of the monomers, without the inclusion of gelatin molecules. In the same year, Lepage et al [2001b] analysed the T_2 dependence of different gel dosimeters using a model of fast exchange of magnetization. In that study the influence of the half-dose and the apparent T_2 of the polymer proton pool on the dose resolution were examined. The concentration of monomers remaining after irradiation can be quantified using NMR spectroscopy and the area under the peaks of acrylamide and bis-acrylamide in the FT-Raman spectra was found to decrease exponentially with increasing absorbed dose. The rate of consumption of monomer was described by a half dose, which is the absorbed dose at which 50% of the monomer molecules have reacted. The influence of the concentration of monomers and gelling agent was subsequently evaluated using a model of fast exchange of magnetisation. The effects of ionising radiation on different compositions of polymer gel dosimeter were investigated by Lepage et al [2001c] using FT-Raman spectroscopy and NMR T_2 relaxation times. They reported that the mobile pool initially contains the protons from water and monomers and they are gradually transferred to the polymer pool upon absorption of ionising radiation. The protons from gelatin in the third pool are unaffected by the absorbed dose. They also reported that the rate of transfer of protons from the mobile to the polymer pool obtained from the NMR data were close to the half-doses determined by FT-Raman spectroscopy. It was shown from their study that the half-dose, and the rate of polymerisation, is greatly influenced by the presence of BIS. The apparent relaxation times of the polyacrylamide polymer and the gelatin change slightly as a function of gel composition. Using the same method, Lepage et al [2001d] investigated the time dependence

of NMR relaxation in PAG dosimeters. They reported that minimal variations in T_2 in an irradiated PAG dosimeter are observed after 13 h.

Using FT-Raman spectroscopy Jirasek et al [2001a] studied the differential rates of consumption of monomer and crosslinker in irradiated PAG. They reported that the consumption is monoexponential up to 13 Gy in both monomer and crosslinker and the sensitivity parameter for bis is smaller than for acrylamide, indicating more rapid consumption of bis than acrylamide in irradiated gel. They also reported that in the 2-10 Gy region, polymer formation observed using Raman spectroscopy is exponential in nature, whereas MRI and x-ray CT dose response curves are linear. Raman spectroscopy offers direct measurement of the concentration of sample constituents, whereas the MRI relaxation times are complex functions of the spectral density of molecular motion. We do not therefore expect to see a direct correspondence between Raman spectroscopy and MRI dose response curve. In another study, Jirasek et al [2001b] reported that monomer consumption rates are dependent not only on initial bis fraction, but also on the radiation dose already absorbed in the gels. Finally, they demonstrated the importance of an existing polymer network on the subsequent monomer consumption rate in a 50%C (initial fraction of crosslinker) PAG. ✓

2.5 Other studies carried out using polymer gel

Polymer gels have been using during the last few years in many different applications. Some of the work has already been reviewed here, but others have not been covered and are reviewed below.

Courbon et al [1999] investigated internal dosimetry for I-131 using a polymer gel in conjunction with MRI. Their preliminary result showed that low dose rate β emitters used in internal dosimetry, like I-131, can be studied using a polymer gel.

Farajollahi et al [2000] used polymer gel for dosimetry calculations for boron neutron capture therapy (BNCT). Their results were compared with calculations using a Monte Carlo program, showing that the absence of boron gave 66.1% and 44.3% of the absorbed dose with boron at depths of 2.5 and 4.0 cm respectively, and their measurement showed that the response of the gel without boron was 65% and 41% of the response with boron at the same depths. Their result indicated that polymer gels may have a role in measuring the

enhancement of absorbed dose due to boron in an epithermal or thermal neutron therapy beam.

Ramm et al [2000] applied BANGTM polymer-gel dosimetry to densely ionising radiation such as carbon ion beams. They irradiated BANGTM polymer-gels with monoenergetic ¹²C ions at different beam energies in the range 135 MeV u⁻¹ to 410 MeV u⁻¹ (u stands for atomic mass unit, MeV u⁻¹ represents normalised energy). They compared MR dosimetry measurement data with data from a planning system, and observed good agreement between the measured dose distributions and the dose map from the planning software. They suggested that the dependence of the efficiency of BANGTM gel on the energy and charge of heavy ions does not allow an absolute dose measurement. ✓

A review article on polymer gel dosimetry was published in the British Journal of Radiology by McJury et al [2000]. In this, they presented a practical overview of polymer gel dosimetry, including gel manufacture, imaging, calibration and application to radiotherapy verification. In 2001 a review article on the applications of polymer gel dosimetry was published by Bonnett [2001]. In this article the application of polymer gel dosimetry such as stereotactic radiotherapy, conformal therapy, IMRT, brachytherapy and particle therapy were discussed together with methods of comparison of results, absorbed dose measurement, phantoms and gel manufacture.

Polyacrylamide gel was studied by Wojnecki et al [2001] for its physical properties as a substitute for brain tissue and compared with standard phantom materials in use for BNCT dosimetry. The polyacrylamide gel gave results that compared very well with standard phantom materials and it could be used as a BNCT phantom material and for dosimetry.

Gochberg et al [2001] measured magnetization transfer and NMR relaxation rates for water protons in polymer gel in order to quantify the contributions of different relaxation processes to the radiation response in gels. A model of relaxation in irradiated gels which incorporates three proton pools: free water, macromolecular and interfacial was presented to explain their properties. They reported that radiation induced polymerisation appeared to increase the size of a solid-like macromolecular proton pool, but that dose not affect the rate constant of magnetisation transfer per proton from macromolecular protons to the free water protons. They also reported that the rate of magnetisation transfer is not limited by the rate of

chemical exchange between the free water and the interfacial protons, and magnetisation transfer most probably occurs via labile proton exchange rather than via bound water molecules.

In 2002 Jirasek et al [2002] characterised a clinically relevant 74 MeV proton beam using PAG gel and measurement was made using FT-Raman spectroscopy. In that study PAG was exposed to the central and end portions of a spread out Bragg peak (SOBP). Their result indicated that the gel is less sensitive to proton irradiation than to x-ray radiation, and that the gel exhibits a differential response between the mid and end region of SOBP. They reported that preliminary differences in response are attributed to the large doses deposited by delta rays closed to the track of the proton, causing detector elements (gels) to saturate, particularly in the end region of the SOBP. Finally, they reported that this study illustrates the difficulty in using polyacrylamide gel to extract quantitative dose maps when exposed to proton irradiation. ✓

Three-dimensional MRI techniques were employed in VIPAR polymer gel dosimetry by Baras et al [2002]. They reported that the 3-D dose distributions obtained with 3-D MRI methods were in good agreement with the corresponding Monte Carlo calculations for brachytherapy and intravascular irradiations. They also presented a 3-D MRI acquisition method which allows the determination dose distributions within an extended volume of the irradiated gel, while providing adequate spatial resolution and MR scanning times which are shorter than those required for conventional 3-D sequences.

In 2002 Lepage et al [2002] reported the use of magnetization transfer (MT) imaging for polymer gel dosimetry. Their result indicated that the dose resolution was relatively good over a wide range of absorbed doses, and that this is the advantage over multi spin echo evaluation of polymer gel dosimeters, where an optimal dose resolution is achieved over only very limited ranges of doses. They suggested that MT imaging protocols might be developed into a useful tool for polymer gel dosimetry.

2.6 Concluding Remarks

From the above discussion it can be seen that polymer gels are able to measure complex dose distribution in three dimensions, for example in brachytherapy applications [Maryanski et al

1996, McJury et al 1999b, Farajollahi et al 1999, Papagiannis et al 2001], stereotactic radiosurgery [Ibbott et al 1997, Meeks et al 1999, Ertl et al 2000, Pappas et al 2001], intensity-modulated radiotherapy [Oldham et al 1998a, De Deene et al 2000d], and cardiovascular brachytherapy [Amin et al 2001, Baras et al 2002]. There are a number of methods used to extract dose information from dosimeters. These include MRI [Gore et al 1984, Maryanski et al 1993], optical tomography [Maryanski et al 1996a, Doran et al 2001a], Raman spectroscopy [Baldock et al 1998b], x-ray computed tomography [Hilts et al 2000] and ultrasound [Mather et al 2002]. It is also clear that gel dosimeters are still not able to measure absolute dose accurately, and that there is still room for improvement in the methodology, particularly in the area of accuracy of dose measurement. More investigation is needed for heavy ions, protons and boron neutron capture therapy.

Chapter 3

MRI

3.1 Introduction

Conventional radiographic techniques, such as CT and nuclear medicine rely on ionising radiation such as x-rays or γ -rays (at the upper end of the electromagnetic spectrum) for investigating the human body. Ultrasound relies on the transmission and reflection of sound energy through tissue. Magnetic Resonance Imaging (MRI) utilizes an entirely different principle, involving the interaction of atomic nuclei with imposed magnetic fields, and the detection of nuclear magnetism using a resonance technique. The nuclei studied in NMR all have odd numbers of protons; the most common nucleus is hydrogen: a single proton.

Originally, the technology was called nuclear magnetic resonance (NMR), referring to the study of minute magnetic properties of the nuclei of some atoms. When the technology developed to the point at which it was used in direct patient care, the “nuclear” part of the title, although descriptively correct, was dropped at the suggestion of the radiology community to allay potential and unfounded fears of radiation hazardous to the general public.

NMR generates very small signals and their strength and frequency give unique information about tissue chemistry. The phenomenon of nuclear magnetic resonance was discovered independently by two groups of workers in 1946, by Bloch at Stanford and Purcell at Harvard. The techniques developed were primarily used to study the structure and dynamical properties of molecules, and subsequently Bloch and Purcell shared the Nobel prize for Physics in 1952.

In the mid 1970's the nuclear relaxation times and properties of tissues were being exploited by Damadian and several other groups, both in the United Kingdom and the United States [Dendy and Heaton 1999]. In the 1970's, and early 1980's, it became clear that NMR could be used to generate more than just test-tube chemical information. Lauterbur proposed that the magnetic resonance (MR) signal could be spatially localized, which made it possible to utilize MR to create images [Lauterbur 1973]. Work on the development of MRI was carried out in parallel by Mansfield et al working in Nottingham [Mansfield 1973 and Grannell 1973]. Since then there has been very rapid development in the number and range of techniques, with the first clinical trials of medical imaging taking place in 1980 [Mansfield and Morris 1982].

The first commercial scanner introduced in 1982, provided spatial information that yielded tomographic sectional images of the human body in the axial plane as in CT, but also in the coronal and sagittal planes, or indeed in any chosen oblique plane. Magnetic resonance images reflect NMR signal changes that are affected by the chemical environment of the hydrogen atoms and the configuration of hydrogen atoms within molecules such as water, fat, proteins and carbohydrates.

3.2 MR Active Nuclei

The phenomenon of nuclear magnetism is not shown by all nuclei; they must contain either an even number of neutrons and odd number of proton or vice versa [Dowsett et al 1998]. MR active nuclei are characterised by their tendency to align their axis of rotation to an applied magnetic field. Due to the laws of electromagnetism, nuclei that have a net charge and are spinning generate a magnetic moment and align with an external magnetic field. The balance between the number of protons and/or neutrons in an atom determines the angular momentum of the nucleus [Lufkin et al 1998]. If a nucleus contains either unpaired protons or neutrons or both, then it has net spin and angular momentum. If there are no unpaired nucleons, the nuclear angular momentum is zero.

Hydrogen atoms, which contain a single proton, are the most favoured nuclei for radiological MRI due to their high concentration in tissue, where around two thirds of all atoms the humans body are hydrogen atoms, and their high gyromagnetic ratio (γ). The gyromagnetic ratio is the ratio of the magnetic moment to angular momentum. In addition to its large relative (chemical) and isotopic abundance in the human body, hydrogen is also highly magnetic, so it yields a high MR sensitivity [Lufkin 1998]. Other physiologically important atoms are ¹³-carbon, ²³- sodium, and ³¹-phosphorus. Each has unpaired protons or neutrons.

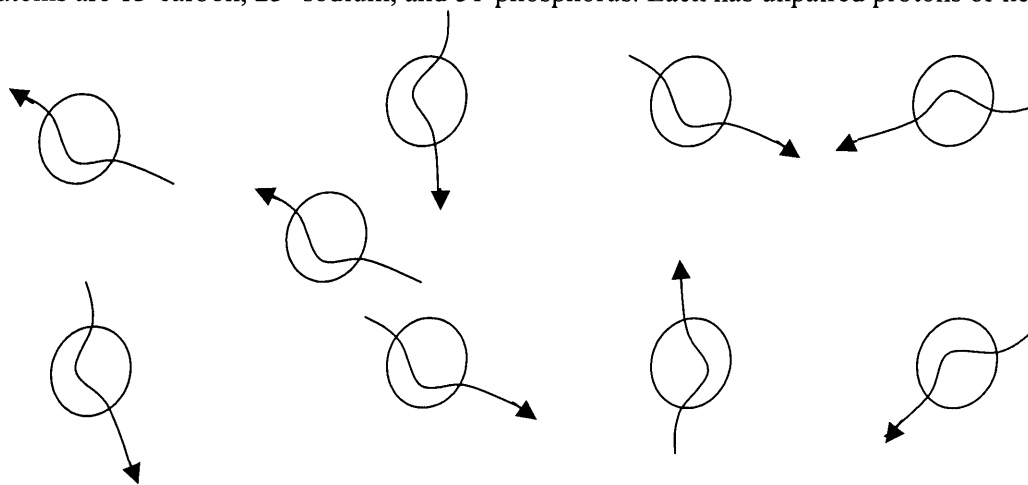


Figure 3.1: A group of proton dipole moments showing different orientations in the absence of an external magnetic field.

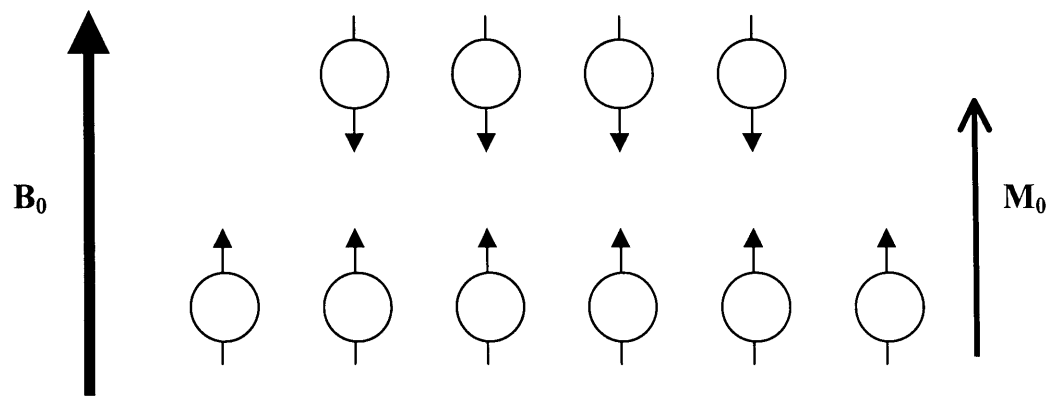


Figure 3.2: The proton axis is aligned in a strong external magnetic field B_0 , and the net magnetization M_0 is parallel to the applied magnetic field vector B_0 .

3.3 The Proton in a Magnetic field

Since the diagnostic imaging application of NMR almost exclusively involves the hydrogen atom, which has at its nucleus a proton with associated angular momentum or spin, the following descriptions will be based on the hydrogen atom as a model. Hydrogen atoms generate a magnetic dipole moment which is analogous to a bar magnet.

In the absence of an external magnetic field, the protons can take any orientation as shown in figure 3.1. When the protons are placed in a strong external magnetic field, the dipole moments of the proton align with this magnetic field. Some of the protons align parallel with the direction of magnetic field, and slightly fewer protons align anti-parallel with the magnetic field as in figure 3.2. The orientation parallel to the applied field is a lower energy state or as it is sometimes called, the ground state. On the other hand, the orientation antiparallel to the applied field is the high energy state, which is sometimes referred to as the excited state. The difference between the numbers of parallel and anti parallel spins depends on temperature but also on the magnetic field strength. As the magnetic field is increased, the energy difference of the states is also increased in favour of the low energy state. If the field strength is approximately 1T, the population difference will be around 3 parts per million [Dendy and Heaton 1999] at body temperature. The population difference can be also increased by cooling the object. The difference in energy and the population difference ultimately affects the signal-to-noise ratio (SNR) in the MR image.

3.4 Precession

When hydrogen nuclei are placed in an external magnetic field B_0 , there is an additional rotation of the nuclei around B_0 field. This secondary rotation is called precession and the speed at which the nuclei precess around B_0 is called precessional frequency. This can be compared with the spinning top or gyroscope in a gravitational field (figure 3.3). The precessional frequency for each nucleus depends on the magnetic field strength and is unique for each nucleus at any given strength of field.

The precessional frequency is governed by the Larmor equation, which states that:

$$\omega_0 = B_0 \times \gamma \quad (3.1)$$

where

ω_0 is the precessional frequency

B_0 is the magnetic field strength

γ is the gyro-magnetic ratio.

The gyromagnetic ratio is the ratio of the magnetic moment to angular momentum and is unique for a particular nucleus.

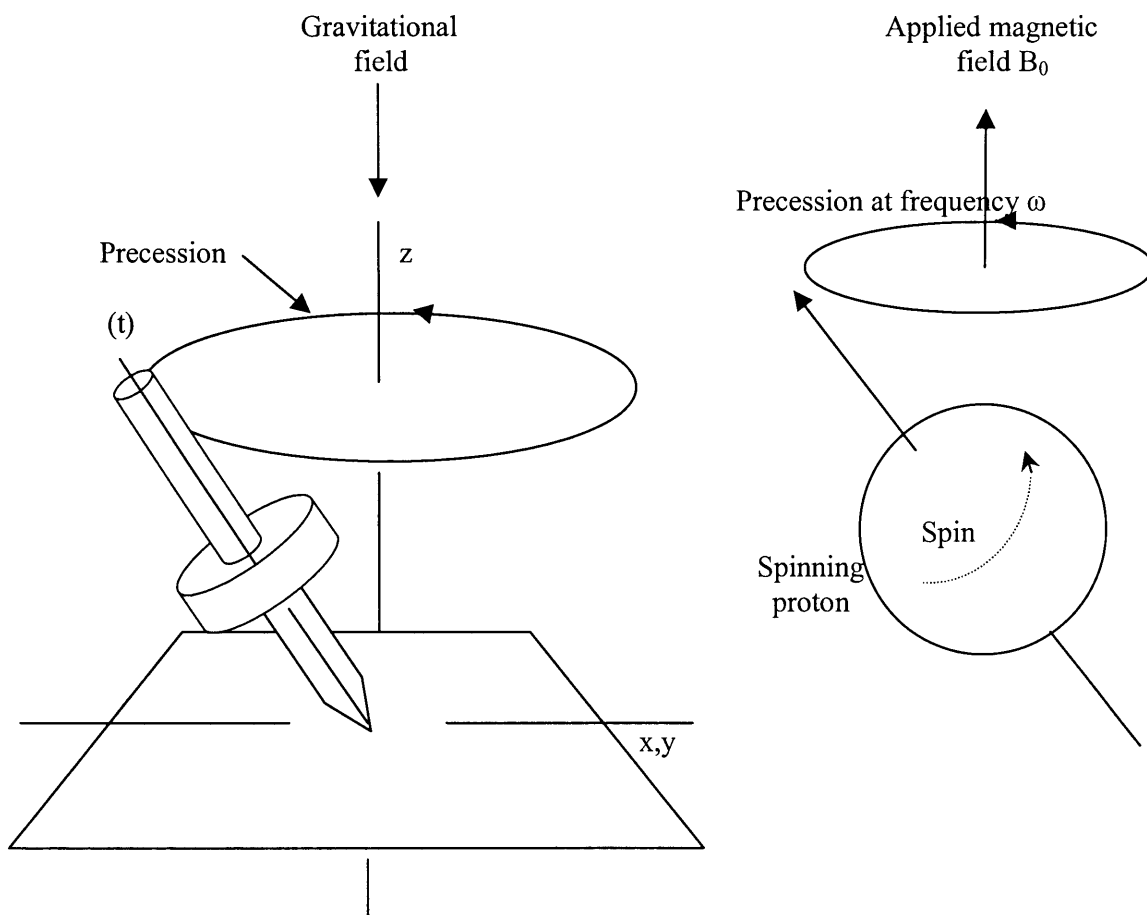


Figure 3.3 The motion of a spinning top in a gravitational field (left) is analogous to the motion of a nucleus in a magnetic field (right).

3.5 Resonance

At equilibrium, the net magnetization M_0 is aligned with the z-axis and is too small to be easily measure directly. This equilibrium state has to be disturbed by the process of resonance before a signal can be obtained.

Resonance is a phenomenon that occurs when an object is exposed to an oscillating perturbation that has a frequency close to its own natural frequency of oscillation. When a nucleus is exposed to an external perturbation that has an oscillation frequency similar to its own natural frequency, the nucleus gains energy from the external source. If the energy is delivered at a different frequency to that of the Larmor frequency of the nucleus, resonance does not occur.

Energy at the precessional frequency of hydrogen at all field strengths in clinical MRI corresponds to the radio frequency (RF) band of the electromagnetic spectrum. In most NMR experiments, the excitation magnetic field is applied in a pulsed mode, and is generally called the RF pulse. This RF pulse changes the direction of the net magnetization vector (NMV) to the transverse plane. This is necessary in MRI, because only the component of the magnetization vector in the transverse plane is detected by the receiver coil as an induced voltage. This voltage constitutes the MR signal.

The result of resonance is that the net magnetization vector moves out of alignment away from z direction. The magnitude of the flip angle is proportional to both the amplitude and duration of the RF pulse [Westbrook and Kaut 1988]. The rotation angle of the magnetization vector following the RF pulse from the longitudinal axis towards the transverse plane is referred to as the flip angle (figure 3.4). If a 90° RF pulse is applied, the net magnetization vector tilts exactly 90° from the longitudinal axis to transverse plane and a 180° pulse causes the magnetization to nutate 180° .

3.6 Relaxation

When the RF pulse is switched off, the NMV is again influenced by B_0 and it tries to realign with it. In order to do so, the NMV must lose the energy given to it by the RF pulse. The process by which the NMV returns to equilibrium is called relaxation, and the characteristic time that it takes is called the relaxation time. Relaxation times are a characteristic of particular nuclei and their chemical environment [Vennart 1985]. As relaxation occurs, the

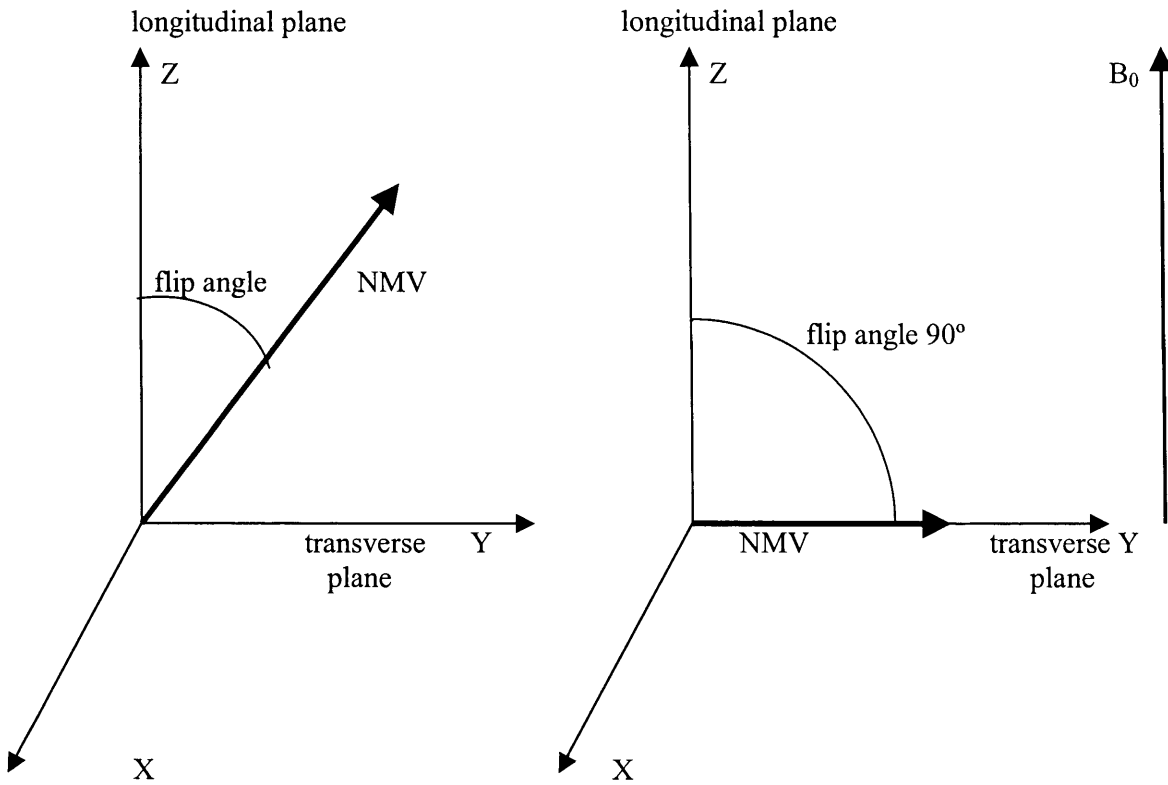


Figure 3.4 Diagram of longitudinal and transverse planes and magnetization vector for different flip angles. NMV = net magnetisation vector.

transverse component of magnetisation is lost, and the NMV returns to realign with B_0 . The process by which the amount of magnetisation in the longitudinal plane gradually increases is called T_1 recovery and at the same time the amount of magnetisation in the transverse plane gradually decreases and this is called T_2 decay.

The T_1 recovery along the z-axis is described by the differential equation

$$\frac{dM_z}{dt} = -(M_z - M_0) / T_1 \quad (3.2)$$

where M_z is the component of magnetisation along the z axis. ✓

This has the solution

$$M_z = M_0 + [M_z(0) - M_0] \exp(-t / T_1) \quad (3.3)$$

T_2 decay of the transverse component, $M_{x,y}$, of the magnetisation vector is described by

$$\frac{dM_{x,y}}{dt} = \frac{-M_{x,y}}{T_2} \quad (3.4)$$

where $M_{x,y}$ is the component of magnetisation in the xy plane. ✓

Which gives the solution

$$M_{x,y}(t) = M_{x,y}(0) \exp(-t/T_2) \quad (3.5)$$

Equation 3.2 and 3.4 are the longitudinal and transverse Bloch equations, respectively.

3.7 T_1 recovery

T_1 recovery is caused by the nuclei giving up their energy to the surrounding environment or lattice. The return of longitudinal magnetization M_z to its equilibrium value requires exchange of energy between the nuclear spins and the material of the lattice. Following excitation by a 90° RF pulse, M_z will return with a characteristic time constant is called the longitudinal relaxation time constant T_1 . The recovery is described by the solution to the longitudinal Bloch equation with an initial condition $M_z = 0$ at $t = 0$:

$$M_z = M_0 [1 - \exp(\frac{-t}{T_1})] \quad (3.6)$$

where t is time and T_1 is known as the longitudinal relaxation time constant or spin-lattice relaxation time. The inverse (T_1^{-1}) of this time constant is called the longitudinal relaxation rate, R_1 .

The value of T_1 depends on the chemical structure of the lattice, on the temperature and on the magnetic field strength. During longitudinal relaxation, the protons lose energy to the surrounding tissue and the rate of energy loss depends on the material or tissue composition. Protons lose energy more rapidly to those tissues with greater complexity or solid tissue such as muscle and protein. As a result, T_1 is shorter for more solid tissues. With simple molecular structures such as water, the energy loss is slower and T_1 is prolonged. Typical T_1 values seen in the human body range between 200 to 3000 ms. The range of T_1 values seen in typical tissues are shown in Table 3.1.

Tissue	T_1 (ms)		T_2 (ms)
	1.0 T	1.5 T	
Fat	240	260	80
Liver	420	500	40
Kidney	590	690	58
Muscle	730	870	45
Heart	750	880	57
White matter	680	780	90
Gray matter	810	900	100
CSF	2160	2400	160

Table 3.1 T_1 and T_2 values seen in typical tissues [Dowsett et al 1998].

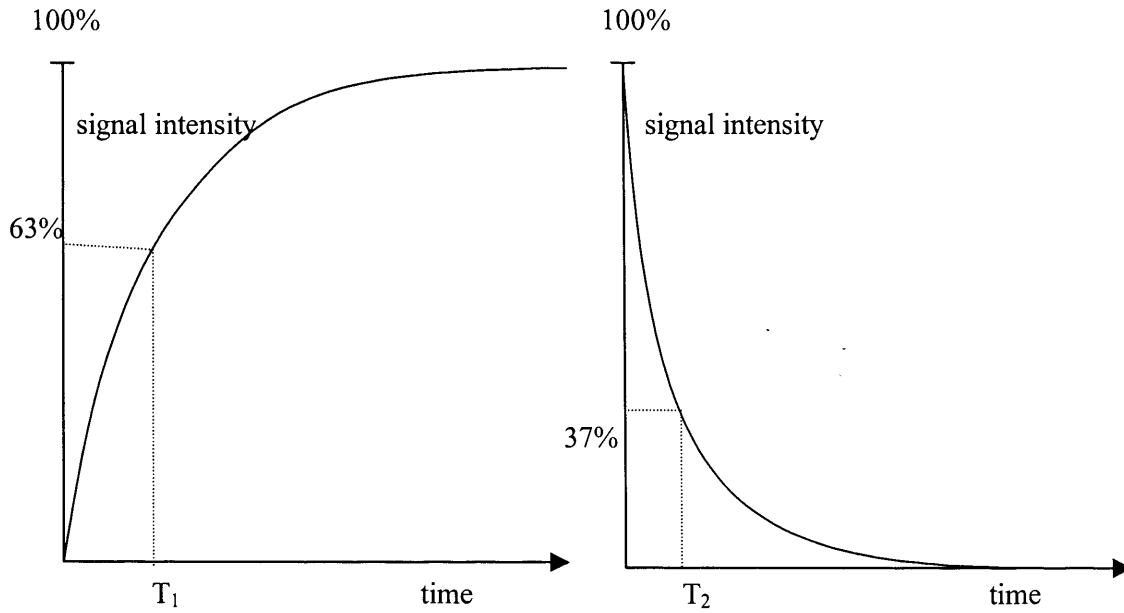


Figure 3.5 (a) Spin-lattice relaxation (T_1) recovery curve. (b) Spin-spin relaxation (T_2) describes the exponential decay of the transverse magnetization. These curves describe the return to equilibrium after disturbance by a 90° R.F. pulse.

3.8 T_2 Decay

T_2 decay involves changes of local magnetic field caused by the presence of neighbouring magnetic particles. Following the RF pulse, the signal will start to decay due to the loss of the phase coherence of the individual spins in relation to one another. The loss of phase coherence results from the fact that the spins are not all precessing at exactly the same frequency. If the spins were precessing continuously at the same frequency they would remain in the phase and the signal would persist with a constant strength. However, nuclear and non nuclear particles (a major contribution to relaxation is from electrons) contribute a small additional field to their neighbours, which results in a slight difference in the frequency of each individual spin relative to the mean, causing dephasing and consequently decay of the transverse magnetisation. This is often termed spin-spin relaxation. Relaxation in the transverse plane is exponential (Figure 3.5) governed by T_2 , the transverse relaxation time constant or spin-spin relaxation time constant. The following equation describes the loss of transverse magnetisation, and therefore signal following a 90° pulse:

$$M_{xy} = M_0 \exp(-t / T_2) \quad (3.7)$$

T_2 can be estimated by plotting $\ln(M_{xy})$ against t , since:

$$\ln(M_{xy}) = \ln(M_0) - t/T_2 \quad (3.8)$$

The slope of this plot yields T_2 . Typical T_2 values for different human tissues are given in Table 3.1.

3.9 T_2^* and Free Induction Decay (FID)

The amplitude of the detected MR signal after a 90° RF pulse does not persist but actually rapidly decays to zero. This damped oscillating signal is called a free induction decay or FID. T_2^* decay is the time constant for decay of the FID following the RF excitation pulse. This decay is faster than T_2 decay since it is a combination of two effects: (1) T_2 decay itself and (2) dephasing due to magnetic field inhomogeneities.

The signal decays rapidly because all magnetic fields are not perfectly uniform, and protons in the sample in slightly different areas of the magnet experience slightly different magnetic field strengths. The Larmor frequency of a nucleus is proportional to the magnetic field strength it experiences, so that for a nucleus in an area of higher field strength, the precessional frequency of the nucleus is increased, while a nucleus in an area of lower field strength has a lower precessional frequency. These relative differences in Larmor frequency, as a result of magnetic field inhomogeneities present in certain tissues, cause dephasing of the NMV. This dephasing is predominantly responsible for T_2^* decay. Dephasing due to inhomogeneities is not necessarily exponential; it depends on the distribution of inhomogeneities.

3.10 Pulse sequences

The subtle differences in tissue chemistry can be thoroughly explored by exposing them to a series of RF-pulses in different sequences, altering their strength and the time interval between them. For many years the most commonly used sequences in magnetic resonance have been the spin-echo and inversion recovery sequences.

The signal strength or brightness of a MR image depends on several parameters such as the timing parameters TE, TR, TI of pulse sequence (see later), the transverse and longitudinal relaxation time of sample, the proton density and motion of the sample, and the properties of the imaging system such as coil type, magnetic field strength etc. Therefore the signal intensity can be written as:

$$S = f(T_1, T_2, \rho, TE, TI, TR) \quad (3.9)$$

Alteration of these parameters results in changes in signal intensity and consequently apparent contrast changes in MR images [Hardy et al 1985, Kjos et al 1985]. There are also several sources of non-uniformity in the signal intensity i.e. non-uniform RF pulses, magnetic field instabilities and inhomogeneities, and uncompensated gradient eddy currents [Kiær et al 1987, Simmons et al 1994].

The following section describes some of the pulse sequences that are important in NMR imaging.

3.10.1 Spin-echo sequence

The spin echo pulse sequence utilises a 90° excitation pulse to flip the NMV into the transverse plane. The protons in the transverse plane then precess in-phase. When the 90° RF-pulse has ended, a FID is produced. T_2^* dephasing occurs immediately, and the signal begins to decay.

Some spins will be precessing faster and others slower due to the inhomogeneities in the magnetic field and because of intrinsic T_2 relaxation. If after a short time, a 180° pulse is applied, reversing the phase of the spins so that those that are precessing faster will fall behind the slower precessing spins. Therefore the effect of the inhomogeneities in the magnetic field on the phase of the spins is reversed. The faster spins continue precessing and catch up with the slower spins and they gradually come back into the phase for a short time producing a stronger transverse magnetization and thus an NMR signal, which is called a spin-echo. This echo signal is used in a spin echo pulse sequence (Figure 3.6) which consists of a 90° RF-pulse followed by a 180° RF-pulse, separated in time by an interval of $TE/2$:

$$90^\circ - TE/2 - 180^\circ - TE/2 - (\text{spin echo}) \quad (3.10)$$

The repetition time (TR) is the time to repeat the sequence of pulses that creates the MRI signal, and is measured in milliseconds (ms). The TR determines the amount of longitudinal relaxation that is allowed to occur between excitations of the longitudinal magnetisation. This longitudinal magnetisation is rotated into the x-y plane by the next R.F. pulse and therefore determines the amount of signal at the next excitation.

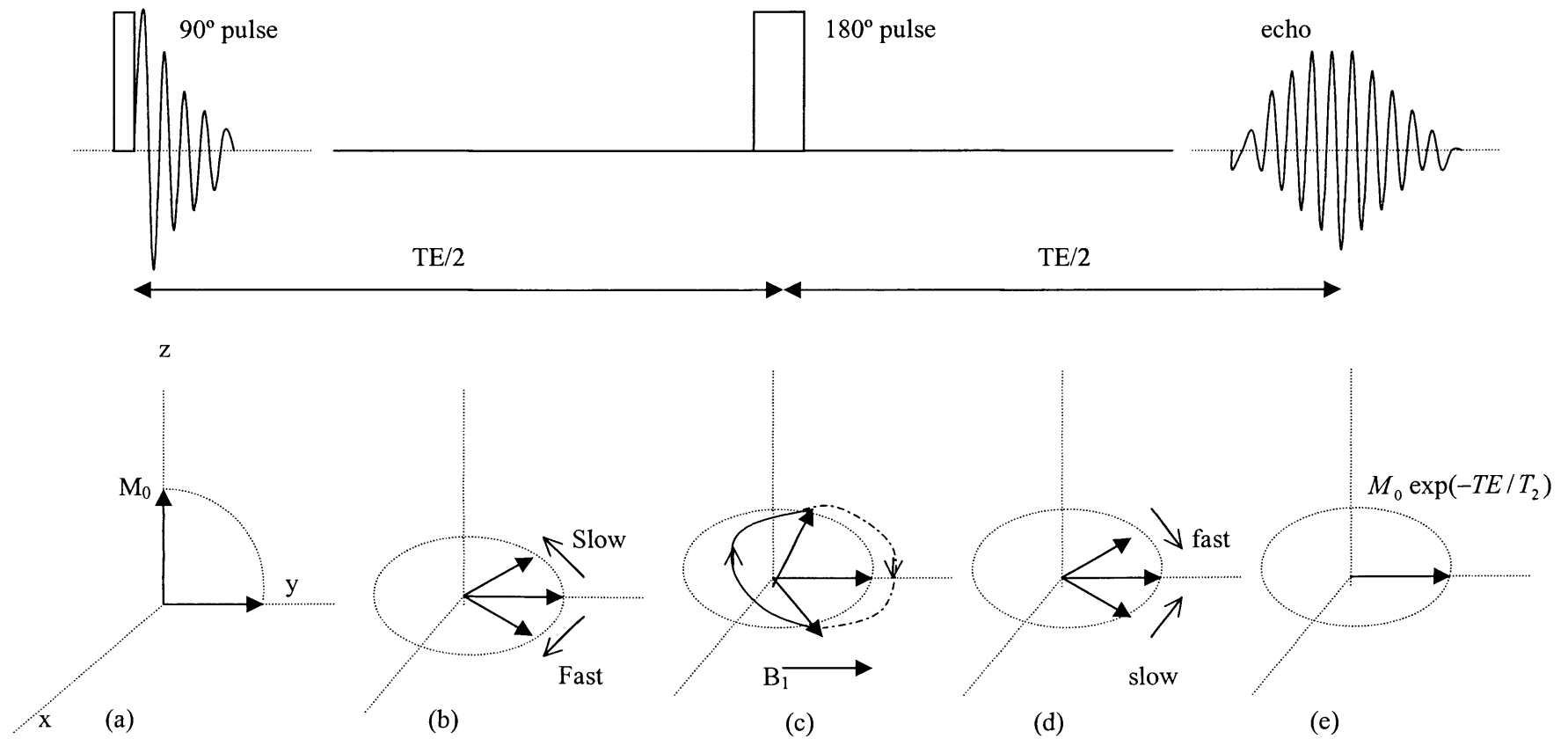


Figure 3.6: (a) The initial 90° pulse flips the magnetization into the transverse plane, where (b) it begins to dephase. (c) At time $TE/2$ the 180° pulse (B_1) is applied which flips all the magnetization over. (d) The protons now begin to rephase, producing a spin echo (e) at time TE .

The echo time (TE) is the time from the application of the exciting RF pulse to the peak of the signal induced in the coil and is also measured in ms. The TE determines how much decay of transverse magnetisation (T_2 relaxation) is allowed to occur before the signal is read.

Magnetic resonance signals are influenced by three major parameters:

- ❖ The nuclear density (number of protons per unit volume)
- ❖ The longitudinal relaxation time T_1
- ❖ The transverse relaxation time T_2

These three qualities are dependent on the tissue type and with a spin-echo pulse sequence, the NMR signal S is given by:

$$S \propto \rho \times (1 - e^{-\frac{TR}{T_1}}) \times e^{-\frac{TE}{T_2}} \quad (3.11)$$

where TR and TE are the repetition and echo time respectively and ρ is the spin density. The formula indicates that TR and TE settings significantly influence image contrast, controlling the part played by T_1 and T_2 relaxation and producing T_1 or T_2 weighted images. Optimum image contrast depends on the selection of TR and TE timing such that the significance of the tissue of interest and or pathology is made brighter or darker than the background tissue. Image contrast is determined by the variation of these parameters to yield T_1 and T_2 weighted images or simply proton density images. This contrast relationship can be summarized as follows:

1. Images acquired with short TR ($TR \sim T_1$) and short TE ($TE \ll T_2$) are T_1 weighted.
2. Images acquired with long TR ($TR \gg T_1$) and short TE ($TE \ll T_2$) are proton density weighted.
3. Images acquired with long TR and long TE ($TE \sim T_2$) are T_2 weighted.

As an example of the application of T_1 weighting, we consider what happens in an image containing both fat and water. The T_1 relaxation time of fat is considerably shorter than the T_1 of typical tissue water. With a short TR, the longitudinal component of magnetisation of fat is larger than water just before the RF excitation pulse is applied; the RF excitation pulse flips the longitudinal magnetisation of both fat and water into the transverse plane. Since

there is more longitudinal magnetisation in fat before the RF pulse, there is more transverse magnetisation in fat after the RF pulse, so fat therefore has a higher signal and appears bright on T_1 weighted images. On the other hand, there is less longitudinal magnetisation in water before the next RF pulse, so there is less transverse magnetisation after RF pulse. Water therefore has a low signal and appears dark on a T_1 weighted images.

A T_1 weighted image is one where the contrast depends predominantly on the differences in the T_1 relaxation times of different tissues. Because the TR controls how far longitudinal magnetisation can recover before it is excited by the next RF pulse, to achieve T_1 weighting the TR must be short enough so that the magnetisation does not have sufficient time to return to the longitudinal direction fully. If the TR is too long, all tissues recover their longitudinal magnetisation fully, the differences in their T_1 relaxation times are not demonstrated on the image (Figure 3.7).

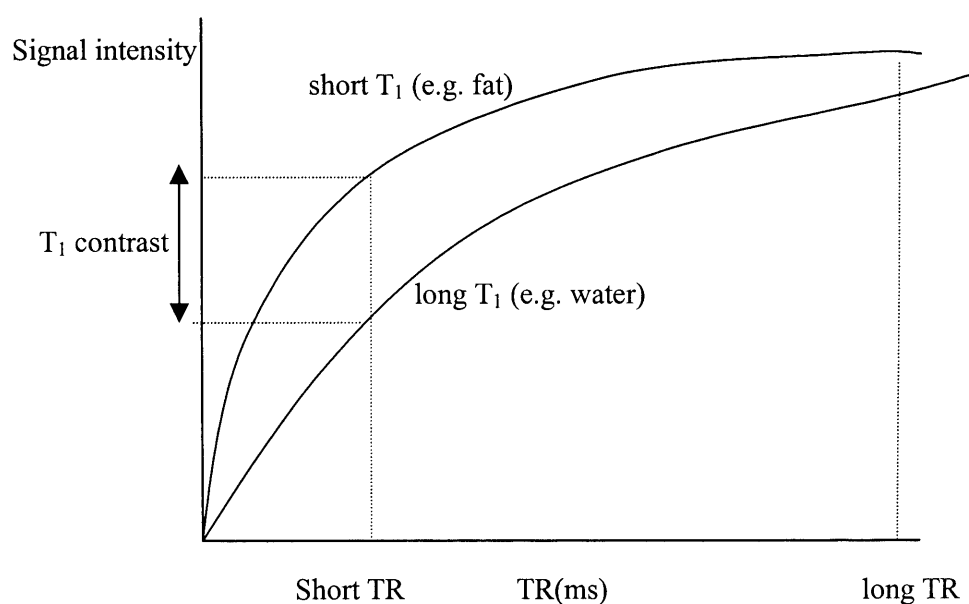


Figure 3.7 T_1 contrast is determined by the TR when there is variation in T_1 between different tissues.

A T_2 weighted image is one where the contrast predominantly depends on the differences in the T_2 between different tissues. The TE controls the amount of T_2 decay that is allowed to occur before the signal is received. Figure 3.8 shows that signal is highest at short TE, but tissue contrast is poor at short TE. As the TE is lengthened, differences in T_2 produce differences in tissue signal intensities. Therefore, tissue contrast improves as TE is lengthened. However, after a certain point, lengthening TE actually worsens tissue contrast,

because all tissue signals become small, and their differences may be masked by background noise. In general, the best T_2 contrast is obtained when TE is intermediate between the T_2 relaxation times between tissues.

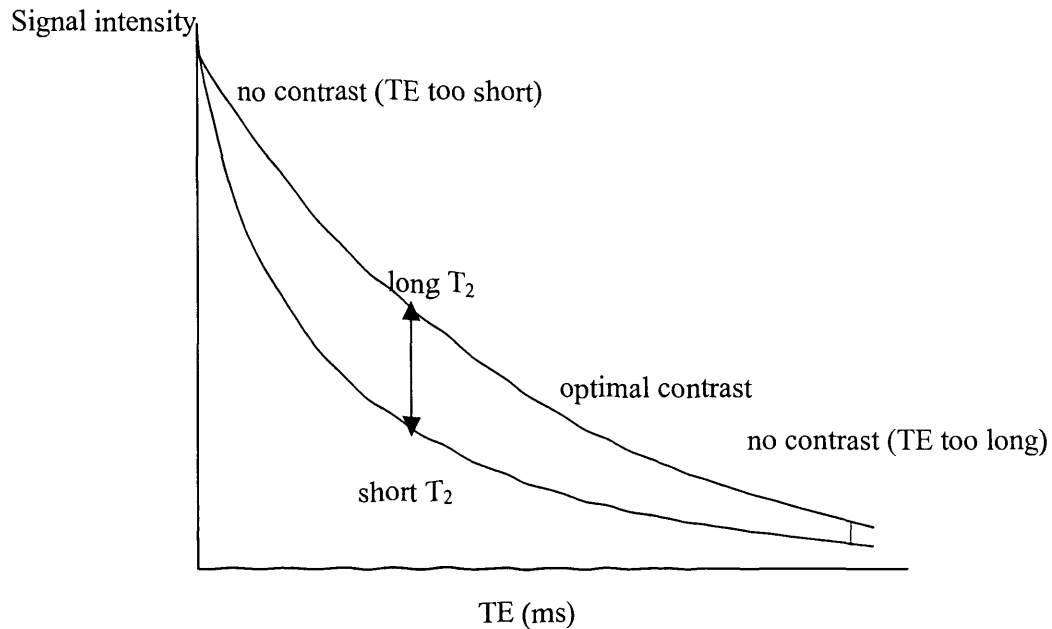


Figure 3.8 T_2 difference fat and water.

3.10.2 Gradient echo pulse sequence

A gradient echo pulse sequence utilizes only a single RF pulse, as represented by

$$\alpha - TE - (\text{gradient} - \text{echo})$$

and the magnitude of the signal given by

$$M_{xy} = M_0 \sin(\alpha) \quad (3.12)$$

where α is an RF pulse with a flip angle usually less than 90 degrees which allows a shorter TR to be used compared to a spin-echo sequence, and M_{xy} is the signal intensity. The formation of an echo with this sequence requires the application of two gradient pulses (Figure 3.9). The application of the frequency-encoding gradient during the echo immediately dephases the spins along the x-direction. To correct for this dephasing, an inverted gradient pulse is first applied prior to read-out, which produces a compensatory phase shift of opposite sign. The first pulse is called a dephasing gradient and the second pulse a rephasing gradient. The pair of dephasing and rephasing gradients constitutes a

gradient reversal, which results in the formation of a gradient echo at the echo time. The loss of signal between the α pulse and the echo is governed by the time constant T_2^* not T_2 .

Unlike conventional spin-echo pulse sequences, which use a 90° flip angle for excitation and 180° refocusing pulse, the flip angle may be freely varied since no 180° refocusing pulse is used for gradient-echo imaging. Using the gradient echo technique, faster imaging is possible than with spin echo sequence, since the TR can be reduced in line with reductions of the flip angle, while still maintaining the same T_1 contrast. This feature is useful for the imaging of dynamic processes.

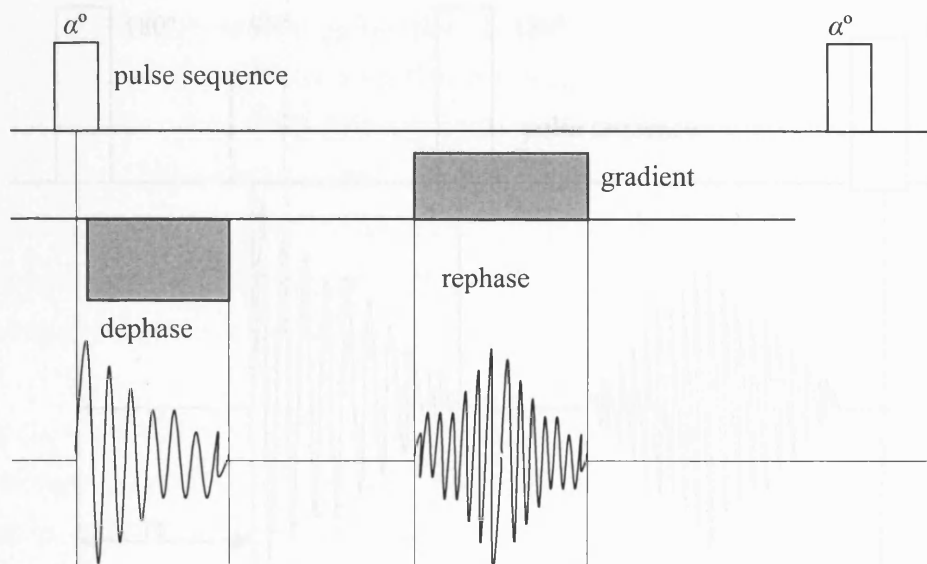


Figure 3.9: Gradient echo sequence which can replace the spin-echo sequence; the reversal of the gradient performs the same function as a 180° RF pulse.

3.10.3 Inversion recovery sequence

The inversion recovery sequence produces a signal that contains more T_1 contrast than the standard saturation recovery sequence. The inversion recovery (IR) sequence has three RF pulses and basically consists of an initial 180° RF pulse followed by a spin-echo sequence (Figure 3.10):

$$180^\circ \text{ -- TI -- } 90^\circ \text{ -- TE/2 -- } 180^\circ \text{ -- TE/2 -- (spin echo)}$$

If the spins are at equilibrium and the net magnetization is aligned with the external field, then the application of a 180° pulse causes inversion of the longitudinal magnetisation. During the recovery period the negative magnetization ($-M$) passes through zero on its way back to equilibrium along the $+z$ axis. No signal is generated, since there is no transverse magnetization. In order to obtain an MR signal, the IR sequence uses the same pulses as a spin-echo sequence after the initial inversion pulse. The time period between the initial 180° RF-pulse and the 90° pulse is the inversion time (TI), also known as τ . The main difference between the IR sequence and the saturation-recovery sequence is that while the saturation-recovery sequence can reduce the magnitude of the signal due to T_1 weighting, the IR sequence can reduce the magnitude of one selected tissue type to zero by selecting TI so that this tissue's longitudinal magnetisation is passing through zero when the 90° pulse is applied.

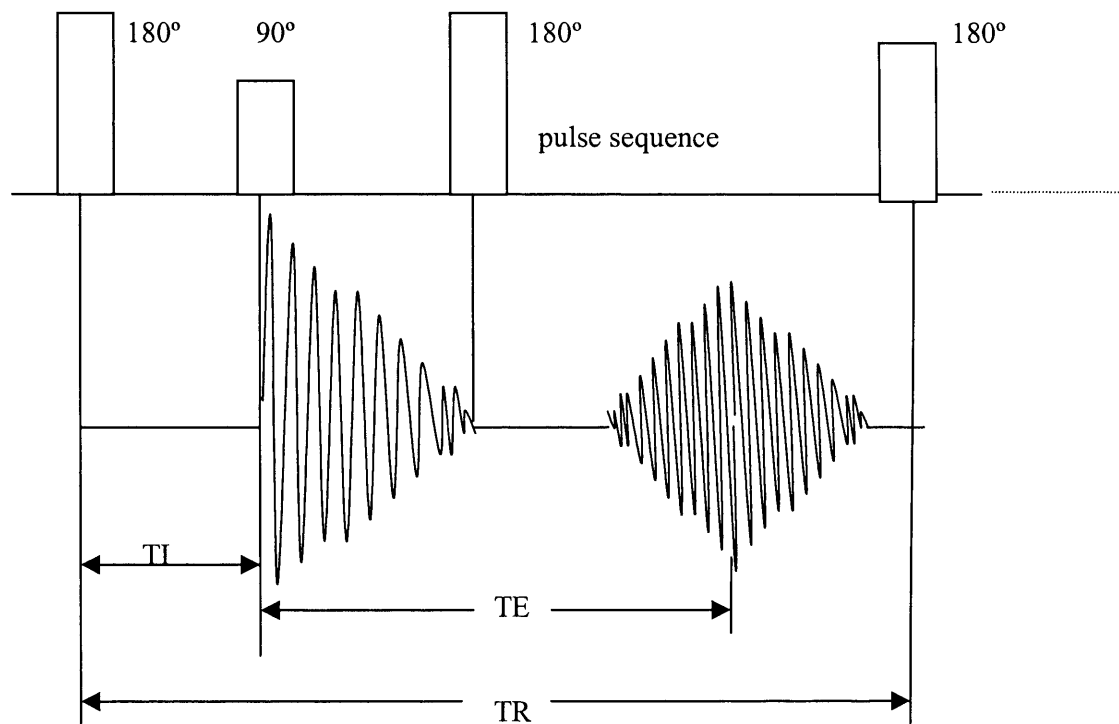


Figure 3.10: Inversion recovery pulse sequence.

3.11 Relaxation measurements

3.11.1 Measuring T_1

Longitudinal relaxation cannot be measured directly. It can be measured by the use of either the saturation recovery or inversion recovery sequences. Between these, the inversion recovery method is considered to be more accurate than saturation recovery. The accuracy of T_1 measurement depends on the number of points measured along the recovery curve: a minimum two readings are taken to obtain minimum accuracy. To improve accuracy,

measurements are done at more TI values, or signal averaged. In order to calculate T_1 the amplitude of the signal is measured for different values of TI, and an expression of the form

$$S(TI) = S_0 (1 - 2\exp(-TI/T_1)) \quad (3.13)$$

is fitted to the data by non-linear least-squares regression, yielding T_1 as one of the fit variables.

3.11.2 Measuring T_2

The simple free induction decay (FID) will be influenced by both proton spin-spin interactions (a property of the tissue) and magnetic field inhomogeneities to give the T_2^* value. If a 180° RF-pulse is applied then this dephasing can be reversed and the signals will re-phase to give full signal intensity: this is spin-echo sequence and was introduced by Hahn in 1950 [Hahn 1950]. With the Hahn spin-echo sequence, the intrinsic rate of dephasing resulting from the sample properties can be measured providing that there is no diffusion of spins. In practice, diffusion of the spins does occur and causes the nuclei to experience different magnetic fields through the inhomogeneous external field, and the precision of the T_2 measurement is therefore affected by diffusion.

To overcome this problem Carr and Purcell (CP) [1954] introduced a modification of the Hahn spin-echo sequence. The 90° pulse is followed by a series of 180° pulses at time interval of $TE/2$: this modification is called the Carr-Purcell sequence (Figure 3.11). For the successful application of the CP sequence it is necessary to have accurate amplitude for the 180° pulses. If there is a small deviation from an exact 180° rotation angle, this will cause an rapidly accumulating error in the echo amplitude [Meiboom and Gill 1958], since, the number of 180° pulses must be large to eliminate the effect of diffusion [Carr and Purcell 1954].

The CP sequence was modified by Meiboom and Gill [1958], a modification known as the CPMG sequence. The only difference between CP and CPMG is the phase of the 180° pulses which stops the error accumulating in long echo trains. In practice 180°_y pulses are used after a 90°_x excitation pulse; this rotates the magnetisation vectors about the y axis thus preventing accumulation of errors due to inaccurate 180° pulses.

In order to measure the T_2 relaxation time accurately, a series of spin-echo images with different echo times is needed. This can be done in 2 ways: repeated single-echo, or multi-echo. However, the inherent problem with the single echo technique when measuring T_2 values is the diffusion of the spins, which occurs during the period between pulse application and echo formation in the medium. This gives rise to a signal loss, particularly at long echo times. Furthermore, this technique relies on accurate 90° and 180° pulses, otherwise T_2 values will be underestimated. On the other hand, for the multi echo sequence, due to the regular phase reversal and refocusing, the coherence loss for the diffusing spins is reduced. However, a number of technical difficulties associated with this approach have been reported in numerous papers [Majumdar et al 1986a,b, Majumder and Gore 1987, Crawley and Henkelman 1987, Czisch et al 1997]. The inaccuracies of the 90° and multiple 180° pulses propagate through the echo train resulting in a complex combination of transverse magnetisation being lost to the longitudinal magnetisation, thus resulting in a signal loss and stimulated echoes, originating from longitudinal magnetisation, giving rise to a signal increase in later echoes. Static field inhomogeneities as well as RF pulse imperfections corrupt T_2 quantification. However compared with the single echo technique, the multi echo technique can acquire a T_2 map several times faster.

3.12 Magnetic Resonance Imaging

So far the discussed has considered how a signal is generated in an NMR experiment. However, what is really required is an image that shows the spatial distribution of nuclear spins in 3-dimensional space. The system must be able to locate the signal spatially in three dimensions, so that it can position each signal at the correct point on the image. In conventional multi-slice imaging, slice selection ensures that only signal from one slice (or plane) is excited and received. Once a slice is selected, the signal is located or encoded along both axes of the slice. All these tasks are performed by using magnetic field gradients.

✓
The NMR signal frequency is directly related to the magnetic field strength by the Larmor equation. A carefully shimmed MRI magnet has a very homogeneous magnetic field so water protons will all have the same Larmor frequency.

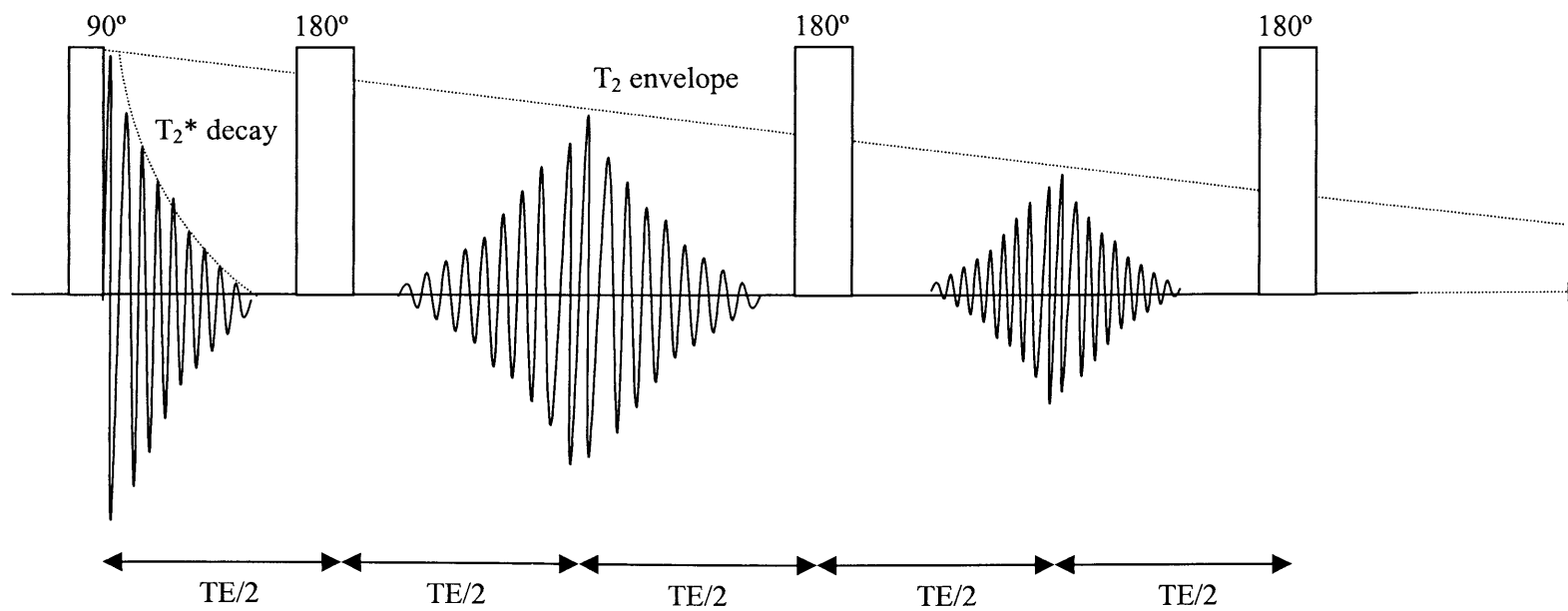


Figure 3.11 The CP pulse sequence.

If a magnetic field gradient G is superimposed on the main magnetic field B_0 so that there is a small linear increase with distance along the gradient direction, then the Larmor frequency for the proton will vary along this gradient as:

$$\omega = \gamma (B_0 + G_z z)$$

where G_z is the added magnetic field from the gradient, in this case in the z -direction. Only those protons in a slice at location z will resonate at a particular frequency ω_s , given by:

$$z = \frac{(\omega_s - \gamma B_0)}{\gamma G_z}$$

Specially constructed gradient field coils are placed within the main magnet and superimpose a uniform magnetic field gradient on the main magnetic field. This gradient field is very small, typically 5mT to 15 mT over the main field of 1T. The main magnetic field must be uniform otherwise the small variations imposed by the gradient fields will distort the image. The gradient magnetic field gives a central null point (Figure 3.12) with a reduced (negative) and increased (positive) magnetic field either side of its null point.

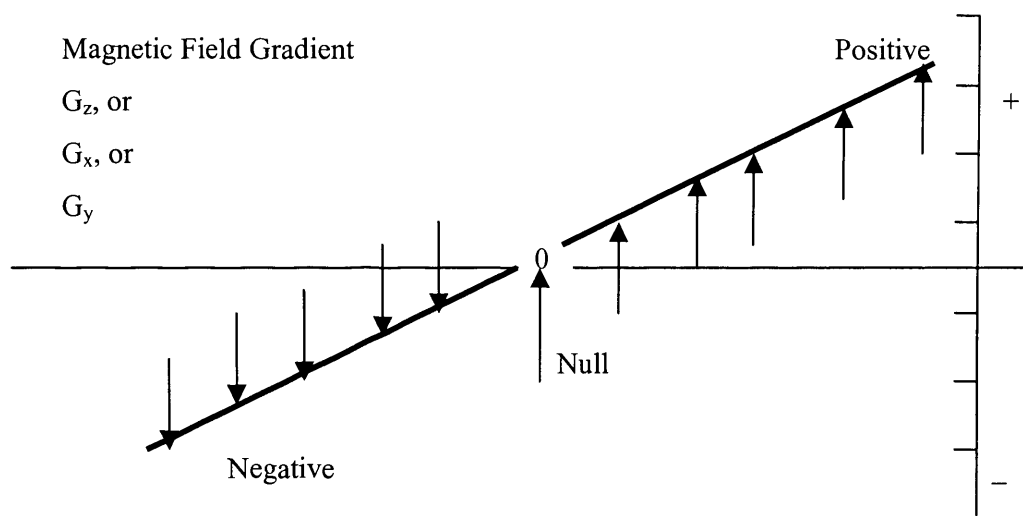


Figure 3.12 Superimposing a gradient field on the main magnetic field. The gradient has a central null point; to one side the field linearly decreases in strength and to the other it increases.

Gradients perform many important tasks during a pulse sequence. As previously described, gradient can be used to either dephase or rephase the magnetic moments of nuclei. Gradients also perform the following three main tasks in encoding.

- (1) Slice selection – positioning the scan plane.

- (2) Spatially locating (encoding) signal along the first axis of the imaging plane – this is called frequency encoding.
- (3) Spatially locating (encoding) signal along the second axis of the imaging plane - this is called phase encoding.

When a gradient coil is switched on, the magnetic field strength, and therefore the precessional frequency of nuclei located along the direction of the gradient varies, in a linear fashion, so that a specific point along the axis of the gradient has a specific precessional frequency. A planar slice situated at a certain point along the axis of the gradient and perpendicular to that axis has a particular precessional frequency. A slice can therefore be selectively excited, by transmitting RF with a band of frequencies coinciding with the Larmor frequencies of spins in a particular slice as defined by the slice select gradient. Resonance of nuclei within the slice occurs because RF appropriate to that position is transmitted. However, nuclei situated in other positions along the gradient do not resonate, because their precessional frequency is different. (Figure 3.13a.).

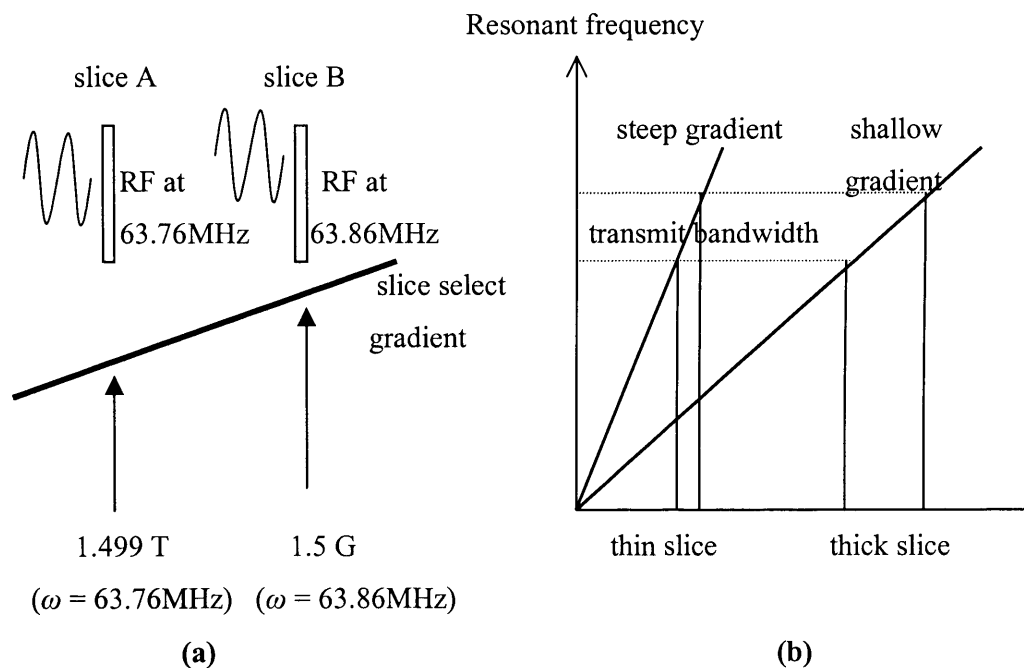


Figure 3.13 (a) Slice selection of two different slices by applying R.F. pulses with 2 different frequencies (b) Transmit bandwidth and gradient slope versus slice thickness.

To give each slice a finite thickness, a band of frequencies must be excited by the excitation pulse. The slope of the slice-select gradient determines the difference in precessional frequency between two points along the gradient. Once a gradient of a certain slope is

applied, the RF pulse transmitted to excite the slice must contain a range of frequencies to match the difference in precessional frequency between the two extreme edges of the slice. This frequency range is called the bandwidth, and since the RF is being transmitted at this point the frequency range is called the transmit bandwidth (Figure 3.13b). To achieve a thin slice, a steep gradient or a narrow bandwidth is applied while to achieve thick slice, a shallow gradient or a broad transmit bandwidth is applied [Chakeres and Schmalbrock 1992]. In a spin echo pulse sequence, the slice select gradient is switched on during the application of the 90° excitation pulse and during the 180° rephasing pulse, to excite and rephase each slice selectively (Figure 3.14).

Once a slice has been selected, the signal coming from it must be located along both axes of the image. The signal is located along the first axis by a process known as frequency encoding. When the frequency encoding gradient is switched on, the magnetic field strength and therefore the precessional frequency of the signal along the axis of the gradient, is altered in a linear fashion. The signal can therefore be located along the axis of the gradient according to its frequency.

The frequency encoding gradient is switched on when the signal is received and is often called the readout gradient. The echo is usually centered in the middle of the frequency encoding gradient, so that the gradient is switched on during the rephasing and dephasing part of the echo as well as the peak (Figure 3.14). The steepness of the slope of the frequency encoding gradient determines the extent of the anatomy covered along the frequency encoding axis during the scan. This is called the field of view (FOV) in the readout direction. Two things determine the FOV in the readout direction:

- 1) The gradient strength (G)
- 2) The time between samples of the NMR signal (δt).

$$FOV \propto 1 / \Delta k, \quad (3.14)$$

where $\Delta k = G \cdot \delta t$.

Signal must be located along the remaining axis of the image and this localization process is called phase encoding. Consider a row of protons precessing at ω_0 in a main magnetic field B_0 . There will be no phase coherence in respect of their precessional motion until a radio-frequency pulse is applied which drives all protons to precess coherently. A magnetic field gradient is applied along the row of precessing protons; each proton will then begin to precess at a slightly different frequency in direct proportion to the local magnetic field

experienced. The differences in precessional frequency between adjacent protons will cause a relative phase shift, which is directly proportional to the differences in frequency, which in turn is directly related to the proton's position in the magnetic field gradient. When the gradient is switched off, all protons will return to the original precessional frequency, ω_0 , but will retain their relative phase shift. This difference in phase between the protons is used to determine their position along the phase encoding gradient. The phase encoding gradient is usually switched on just between the 90° and the 180° rephasing pulses (Figure 3.14). The steepness of the slope of the phase encoding gradient determines the degree of phase shift between two points along the gradient.

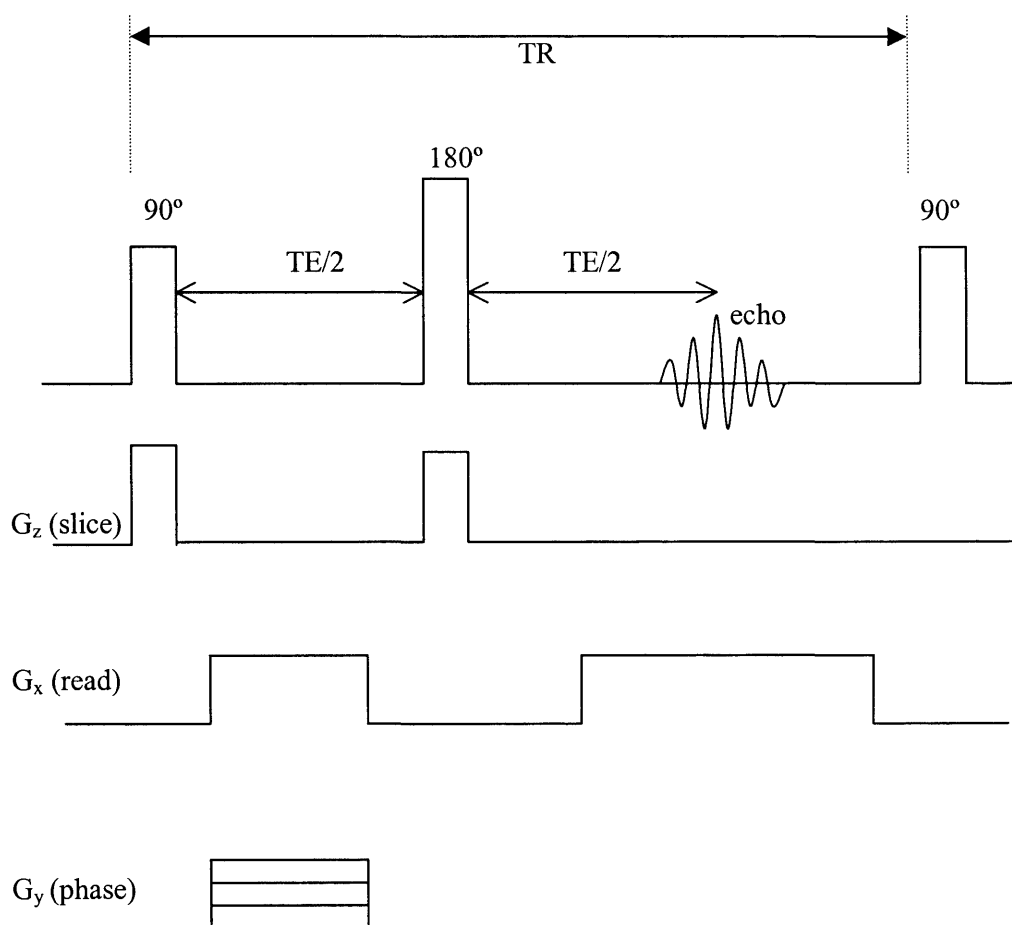


Figure 3.14 Gradient timing in the spin echo sequence. For each repetition of the sequence, the amplitude of the phase-encoding gradient is stepped up.

3.13 Image Formation Matrix

Despite the complexity of the gradient actions necessary to spatially encode the signal that is detected in the echo, that single signal is not enough to make an entire image. Instead this process must be repeated many times. Each repetition is referred to as a phase encoding step. Modern MR instruments typically acquire from 128 to 1024 of these steps to form an image. The slice select gradient must be turned on the same amount with each view in order to repetitively select the same slice. The readout gradient also remains the same with each of these steps. The only thing that changes between sequence repeats is the phase encoding gradient amplitude, which varies through many different steps from negative, through zero to positive. The low gradient amplitude acquisitions sample low spatial frequency information in the image, and higher gradient amplitude sample its high spatial frequency aspects.

For each sequence repeat, and different phase encoding gradient amplitude, an echo is collected. The echoes are then digitised and loaded into a two-dimensional data acquisition matrix referred to as k space. The data are then Fourier transformed in two dimensions (2D-FT), which maps the phase and frequency information to form an image, and the signal amplitude information for each pixel is displayed as a brightness.

The spatial resolution along the frequency axis is determined by the length of time for which the echo is acquired. If spatial resolution in the frequency axis is to be increased, the signal is subdivided into a larger number of frequency bins. Although there is a decrease in signal to noise, there is virtually no penalty in image acquisition time. An increase in the spatial resolution in the phase encoding axis, however, require more phase encoding steps if the FOV is to remain the same. The problem here is that each phase encoding step takes one repetition time (TR). So, unlike the frequency encoded axis, spatial resolution along the phase axis increases the image acquisition time.

Because of this fact, MR images routinely have higher spatial resolution in the frequency than in the phase encoding axis. Often images are acquired with a 256×192 matrix, with 256 samples of the signal during the readout, and 192 phase encode steps.

In MR imaging there are two major contributions to image noise: (1) the random motion of charged molecules in the body, which produce electromagnetic noise, and (2) the electrical noise of the coil itself. Unfortunately, there is no practical way to reduce the noise in an MR signal. The signal to noise ratio (SNR) in an MR image depends on the amount of signal

from a voxel, with the SNR being proportional to the voxel volume. Thus the SNR depends on a straightforward fashion on the FOV of the image, the slice thickness, and the image matrix size. SNR can be improved by signal averaging: both signal and noise increase with the number of excitations (NEX), but the signal increases in proportion to NEX, while the noise, which is random, increases in proportion to $(\text{NEX})^{1/2}$, as expressed by

$$\text{S/N after signal averaging} = (\text{signal} \times \text{NEX}) / (\text{noise} \times (\text{NEX})^{1/2}) = \text{S/N} \times (\text{NEX})^{1/2}$$

Of course the disadvantage is that signal averaging increases acquisition time in proportion to the number of averages.

Chapter 4

Polyacrylamide gels (PAG) dosimetry

4.1 Introduction

The main aim of radiation therapy is to deliver a sufficient and uniform dose to the target and minimizing the dose to the normal tissue. To provide the best outcomes, different types of irradiation techniques such as intensity modulated radiotherapy, stereotactic radiosurgery and high dose rate brachytherapy are currently being used. For the clinical implementation of these techniques, it is necessary to accurately measure three-dimensional dose distributions with high resolution. Dosimeters currently in use either measure absorbed dose at a single points only (e.g. ionisation chambers) and are labour intensive if high resolution is required throughout a large volume [(e.g. TLD), Ramini et al 1994] or measure a 2D distribution (e.g. radiographic and radiochromic film).

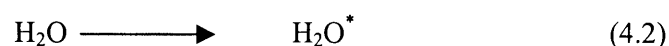
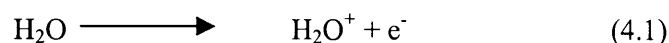
In 1984, it was proposed that magnetic resonance imaging (MRI) could be used to measure dose distributions produced by ionising radiation absorbed in aqueous gels infused with a ferrous sulphate dosimeter solution [Gore et al 1984a]. Although this system provided a number of unique features for dosimetry such as 3-D dose distribution, and tissue equivalence, the major drawback was that the ferric ions were able to diffuse quite freely through the gel after irradiation leading to a blurring of the measured dose distribution.

An alternative type of gel for imaging radiation dose distributions in three dimensions using MRI was developed by Maryanski and co-workers in 1993. This gel did not suffer from the effects of diffusion [Maryanski et al 1993]. The gel was given the acronym BANANA gels. This stands for Bis, Acrylamide, Nitrous oxide, And Agarose. This dosimeter was based on radiation-induced polymerisation and cross-linking of acrylic monomers in a gel matrix. In 1994 Maryanski and co-workers developed another gel, referred to as BANG-1 gel. The acronym was formed from Bis, Acrylamide, Nitrogen and Gelatin [Maryanski et al 1994]. Here, gelatin was used as a gelling matrix instead of agarose, because the transverse NMR relaxation rate of water in a gelatin is nearly an order of magnitude lower than that in agarose gels [Olsson et al 1989, Maryanski et al 1994] and therefore the background R_2 in the gel was substantially reduced which improved its dynamic range [Maryanski et al 1994]. Another advantage of gelatin is that the cooling rate is much slower than that of agarose, giving a more uniform gel [Duzenli 1994, Maryanski et al 1994]. In addition, gelatin is more

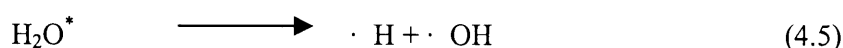
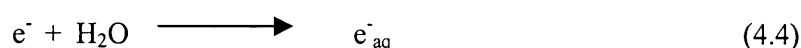
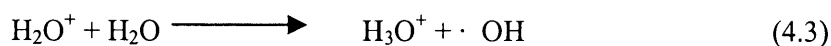
transparent than agarose allowing the polymerised area to be visualised more clearly [Maryanski et al 1994]. In 1996 Maryanski et al reported another improved gel formulation known as BANG-2 where the acrylamide was replaced with acrylic acid. Sodium hydroxide was also added to raise the pH to about 3.5 and they showed that the sensitivity of this gel was higher than BANG-1 [Maryanski et al 1996]. Another supersensitive polymer gel was developed in 1996 by Maryanski et al and called BANG-3 [Maryanski et al 1998] where the crosslinking agent was removed, and methacrylic acid was used as the only monomer. They reported an NMR sensitivity of up to $4 \text{ s}^{-1}\text{Gy}^{-1}$ and the dose response was linear up to 2.3 Gy.

4.2 Radiation induced polymerisation

Ionising radiations deposit their energy into material by inducing molecular ionisations and excitations. The probability of these initial interactions depends on the atomic composition of the absorbing material. Polymer gel dosimeters consist of typically 90% by weight of water and as a consequence, the radiation chemistry of water is of great relevance to the initial reactions that take place in gels. The passage of ionising radiation through water and solutions containing water initially produce electrons (e^-), positively charged water ions (H_2O^+) and excited water molecules (H_2O^*) [Dole 1972, O'Donnell et al 1970].



The electrons lose further energy by collisions until they reach thermal energies and become solvated. The positive ions are energetically very unstable, and decompose rapidly to give H^+ ions and $\cdot\text{OH}$ radicals. The molecules in the excited state are believed to decompose to form radical species.



Where the hydrated electron, e_{aq}^- , is a thermalised electron surrounded by water dipoles.

The above reactions take place within 10^{-9} s of an irradiation. During the diffusion phase (10^{-12} - 10^{-7} s) some of these radicals react with others from the same cluster to form molecular hydrogen and hydrogen peroxide, and reform water.



After 10^{-7} s the radiation-produced free radicals are uniformly distributed in the water after the initial deposition of energy [Appleby 1999].

The above brief discussion has described the primary and longer-lived species produced during the radiolysis of pure water. None of other species present in polymer gel dosimeters are especially susceptible to primary degradation on radiolysis, so that irradiation of dosimeter solutions will result in essentially the species produced in the above reactions. The kinetics of polymerisation involve three distinct stages in such reactions, namely initiation, propagation and termination.

- (a) Initiation: Once the primary radicals ($\text{R}\cdot$) escape from the solvation cage they can react with a monomer molecule, M , to form $\text{RM}\cdot$.



- (b) Propagation: The first chain radical $\text{RM}\cdot$ reacts with a monomer to produce $\text{RM}_2\cdot$ which in turn reacts with a third monomer and so on.



- (c) Termination: The chain radical can be removed from the reaction system, e.g. by combination of two radicals. The propagation of the chains continues until termination takes place. One type of termination occurs when two growing chain radicals react with each other. Alternatively a hydrogen atom can be transferred from one chain to other to form two polymer chains. This mechanism is called disproportionation.



Polymer molecules are then linked together in various ways, among them random cross-linking [Charlesby 1991]. For simple radiation induced cross-linking the number of intermolecular cross-links is proportional to absorbed dose. The formation of each cross-link removes one separate molecule from the population. As the absorbed dose increases, the chance of cross-linking occurring between different parts of the same molecules also increases.

4.3 Toxicity of PAG

There are important safety considerations when handling acrylamide and bis acrylamide, which are neurotoxic [ICN Biomedicals 1999]. Repeated skin contact, inhalation, or swallowing may cause nervous system disorder. Acrylamide can be absorbed through unbroken skin. It has high oral toxicity. Effects are cumulative and irreversible. Intoxication from it has caused peripheral neuropathy, erythema and peeling of the palms. Bis acrylamide also has high oral toxicity and is also irritant. Any contact of the monomer or co-monomer or their solutions with the skin or eyes, or inhalation the vapours must be avoided, so the preparation should be performed taking the appropriate safety precautions i.e. wearing gloves, chemical safety goggles, face mask, laboratory coat and with adequate ventilation, preferably under a fume hood.

4.4 Preparation of PAG

In this study, a polyacrylamide gel (PAG) was prepared. The preparation method followed the procedure of Maryanski et al [1994] with some exceptions. These exceptions were firstly, the gel was prepared in the dark room in order to avoid any possibility of polymerisation by ultraviolet rays. Secondly, the gel was prepared in a reaction flask and only the pouring procedure was carried out in a glove box with a nitrogen environment. Thirdly, the gel was transferred from the reaction flask to the calibration tubes or phantoms in the glove box using nitrogen pressure [DeDeene et al 2000]. A pouring method was also used to transfer gel from the reaction flask to vials or phantoms inside the glove box.

A number of factors have been reported which may be detrimental to the radiation induced polymerisation reaction in PAG type dosimeters. These have been taken into consideration during gel preparation and are described below:

1. Photo-polymerisation was seen to occur by Maryanski et al [1993] in PAG samples exposed to light. Maryanski et al [1999] also used light of several wavelengths and found that this effect is stronger in the ultraviolet region and becomes weaker as the wavelength increases. Therefore, photo-polymerisation degrades the sensitivity of the gel. Shielding of the gel from light is important and this problem can be overcome using good light-tight materials.
2. Monomer and cross-linker concentration in the gel has a significant effect upon the sensitivity of the gel and its upper and lower limit of dose response. Baldock et al [1996] found that PAG gels prepared with higher monomer and cross-linker concentrations gave a higher sensitivity. They also reported that doubling the monomer and cross-linker concentration from 3% to 6% gave an increase in sensitivity from $0.28 \text{ s}^{-1} \text{ Gy}^{-1}$ to $0.56 \text{ s}^{-1} \text{ Gy}^{-1}$. However, if the percentage of the monomer and cross-linker are increased, it takes a longer time for them to dissolve. It was reported that low temperature water is not an ideal solvent for bis [Righetti et al 1983]. Farajollahi [1998] reported that for a gel prepared using 9% of total monomers it was observed that on the top of the gel, crystalline salt was formed one week after preparation but using 8% of total monomer did not result in the formation of crystalline salt.
3. The gel polymerisation process is initiated by free radicals, and molecular oxygen is an efficient scavenger of free radicals. The effect of dissolved oxygen upon the sensitivity of polyacrylamide gels has been reported in a number of papers [Bio-Rad Bulletin 1987, Maryanski et al 1993, Maryanski et al 1994, Baldock et al 1998, Hepworth et al 1999]. It was observed that even trace amounts of oxygen led to a complete failure of the polymerisation reaction, hence, it is important to manufacture gels in an oxygen free environment.

All polymer gel preparations used a gelatine of type A (acid derived), approximately 300 Bloom (a gel strength indicator), obtained from the Sigma Aldrich chemical company. Electrophoresis-grade acrylamide monomer and N, N'-methylene-bisacrylamide cross-linker (bis) were obtained from ICN Biomedical LTD. Deionised water was also used to make the gel. Oxygen free nitrogen gas was used to remove dissolved oxygen from the gel solution. Gelatine, acrylamide and N, N'-methylene-bisacrylamide were weighed in a fume cupboard.

The gel was prepared in a reaction flask. After making the gel, it was transferred from the reaction flask to different calibration tubes and phantoms in the glove box with a nitrogen atmosphere containing less than 0.1 % of oxygen. The composition of the PAG to be manufactured was chosen to be 5% gelatine, 3.5% acrylamide and 3.5% N, N'-methylene-bisacrylamide by weight with deionised water (<1microsiemen) as the remaining constituent.

In order to prepare the required amount of PAG, the necessary volume of deionised water was placed in a reaction flask. This water was first deoxygenated by bubbling oxygen free nitrogen gas through it at a flow rate of 1 litre per minute for around one hour. The flow of nitrogen was ceased temporarily and 5% gelatine (by weight) was introduced into the reaction flask via a funnel. After adding the gelatine, the flask was placed in a 50°C water bath. From this time, nitrogen gas was again passed over the mixture at the same flow rate. When the gelatine was dissolved, the flask was wrapped in aluminium foil in order to protect the gel from daylight. Then the acrylamide and N, N'-methylene-bisacrylamide were added. The mixture was then magnetically stirred until the monomers were dissolved with a nitrogen flow rate of 150 cc/min over the surface. Then the flask was returned to the water bath of temperature around 37°C and bubbled with nitrogen at a flow rate of about 150 cc/min. Vigilance was maintained to ensure that the temperature did not rise above 55°C as this might have caused pre-polymerization within the solution [Baldock et al 1998].

All calibration tubes and the phantom in which the gel was irradiated were also flushed with nitrogen so as to remove all oxygen, and placed in a glove box where the nitrogen concentration was less than 0.1%. This was measured using an oxygen meter [Neotox-xl, Zellweger Analytics]. All tubes and phantoms were wrapped in a lightproof aluminium foil to prevent photopolymerization of the monomer. The polymer gel solution was transferred from reaction flask to the calibration tubes and phantoms in the glove box using nitrogen pressure. A gravitational method was also used to transfer gel from reaction flask to vials or phantoms as shown in Figure 4.1. Finally, the calibration tubes and phantoms were sealed and placed in iced water in the glove box for the gel to solidify.

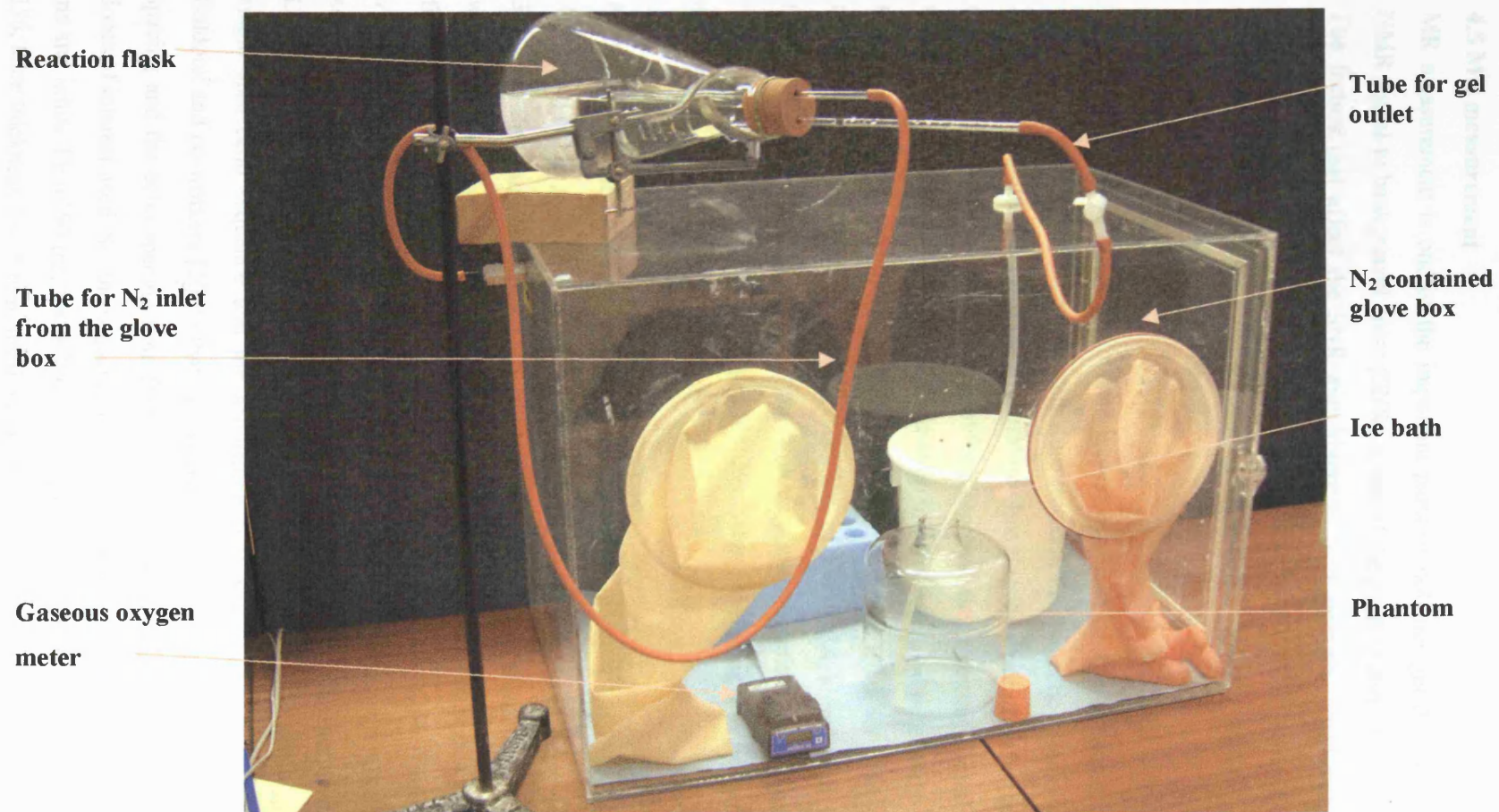


Figure 4.1 Set-up for pouring gel.

4.5 MR measurement

MR measurement is one of the important parts of polymer gel dosimetry and the ratio of NMR signal to background noise (SNR) is one of the most important factors in MR imaging. The factors that affect the SNR are: Magnetic field strength, voxel size, slice thickness, matrix size, signal averaging, receive bandwidth, coil type, inter-slice gap and TR, TE and flip angle [Dowsett et al 1998, Westbrook et al 1988]. So to obtain the best quality MR images it is important to optimise the above factors.

The majority of the images in this thesis were acquired using a Siemens Impact 1T whole body scanner. Once irradiated, the gels were stored in the magnetic resonance (MR) room for 24 hours to equilibrate to room temperature. Imaging was performed approximately three days after irradiation: McJury et al (1999a) reported that imaging should be performed a minimum of three to four days post-irradiation to achieve a good percentage of the maximum attainable sensitivity of the dosimeter. The body coil was used for radio frequency pulse transmission, and the knee coil for reception of the NMR signal. For any single dose measurement, all images were acquired with constant transmitter and receiver gain settings so that image intensities were comparable. No image processing was performed by the MRI scanner.

In this work, both single spin echo sequence and multi-spin echo sequences were used depending on the scanner time that was available. For the single spin echo sequence, a TR of 3000 ms, and four echo times (TE) of 12, 400, 700, 1000 ms were used. A TR of 3000 ms was chosen to allow sufficient longitudinal relaxation to give good signal to noise ratio. The field of view (FOV) was 192 mm and the matrix size was 192×256 . The number of slices varied from 1 to 5 and slice thickness was 2-5 mm depending on the sample size. For this scan, the acquisition time for each echo time was 9 min 40 sec. Baustert et al [2000] and De Deene et al [2002c] reported that the multi-spin echo sequence gave better accuracy than the single spin echo sequence and the acquisition time was shorter. It has been shown by Baldock and co-workers [2001] that the uncertainty of T_2 determination depends on the echo spacing and the echo spacing time 50 ms is more appropriate than <50 ms in the range of doses of interest used. So, the sequence employed an echo train length of 16, echo spacing 50 ms and initial TE of 50 ms, TR = 3000ms, a field-of-view (FOV) 192 mm, matrix size 256×256 , slice thickness 2 to 5 mm, resulting in an acquisition time of 12 min 49 sec. Both single spin-echo and multi spin echo provided an in-plane resolution of 0.75 mm.

4.6 Preparation of the R_2 and dose image

Initially, the T_2 images are in SIE format (Siemens image file format). These images were then transferred from the MRI computer to a Sun microsystems workstation (Palo Alto, CA, USA) where the SIE format images are transferred to Dicom format and then again converted to UNC (University of North Carolina) format for further analysis. The change in nuclear transverse relaxation rate R_2 is proportional to the radiation dose [Maryanski et al 1994]; therefore by measuring R_2 , the dose can be estimated. In a spin-echo MR image, the signal intensity varies according to:

$$S = S_0 e^{-TE \cdot R_2} \quad [4.14]$$

or

$$\ln\left(\frac{S}{S_0}\right) = -TE \cdot R_2 \quad [4.15]$$

where S_0 is the signal intensity at zero echo time. Thus, R_2 was estimated on a pixel-by-pixel basis from the thirteen different echo times [200 to 800ms, an intervals of 50 ms] for the multi-spin echo sequence and four different echo times [12, 400, 700, 1000 ms] for the spin echo sequence, by non-linear regression using the Levenberg-Marquardt algorithm [Press et al 1992] using in-house software. The lowest three echo times for multi-echo sequence (50, 100, 150 ms) were discarded prior to R_2 parameter map construction [Figure 4.2] with the aim of removing error caused by RF pulse imperfections present in the early echoes [McJury et al 1998].

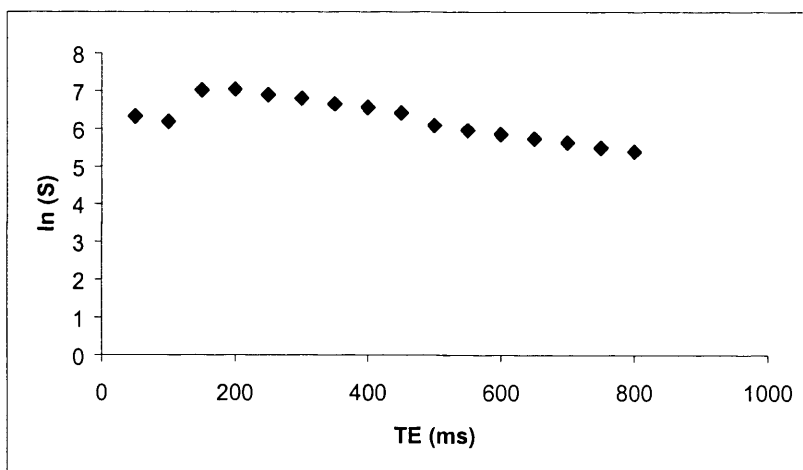


Figure 4.2 Log of signal intensity versus echo times plot for multi spin echo sequence with echo time of 50 to 800 ms of interval 50ms. The step seen between images 9 and 10 was commonly observed; cause of this is unknown.

The relationship between R_2 and radiation dose was established by measuring the R_2 of the calibration samples, and then fitting a straight line of the form:

$$R_2 = R_{2b} + D \cdot \rho \quad [4.16]$$

where R_{2b} is the background R_2 (unirradiated) of the gel; D is the radiation dose; and ρ is the dose response of the gel (slope of the linear portion of the dose response curve). Having established R_{2b} and ρ , subsequent estimations of R_2 as part of a dosimetric measurement allowed an image of radiation dose to be computed. Isodose distributions were drawn using MATLAB (Math Works Inc., Natick, MA). The whole procedures are shown in a flow chart [figure 4.3].

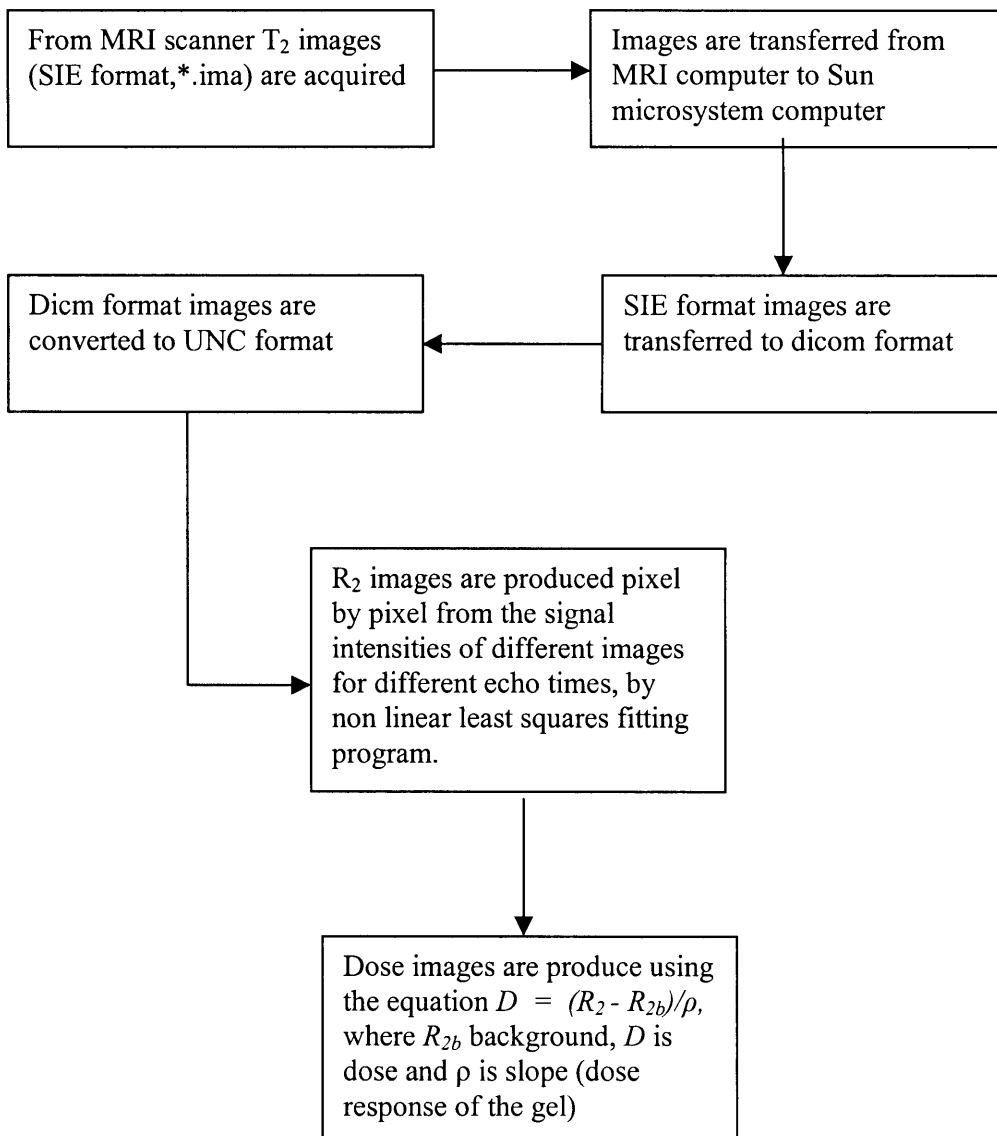


Figure 4.3 Flow chart for preparing dose images.

The ROIs (regions of interest) used to determine R_2 or absorbed dose were circular with a diameter ranging from 10 to 15 mm.

4.7 Oxygen elimination time from deionised water

The gel polymerisation process is initiated by free radical reactions, and molecular oxygen is a scavenger of free radicals. The presence of oxygen in the gel can lead to a complete failure of the polymerisation reaction, so it is important to eliminate oxygen from the gel. The first stage of the manufacture of the gel involves bubbling oxygen free nitrogen gas through the de-ionised water to deoxygenate the water. Estimates were made of the length of time taken to eliminate oxygen from the deionised water. In addition, estimates of the oxygen elimination time were made for different flow rates of nitrogen, and also for different volumes of water.

For this experiment, a conical flask of two litres capacity was used. A rubber bung was used in the flask, and three holes were drilled through the bung. Two lengths of plain glass tube for air inlet/outlet were inserted into the holes. One reached the bottom, dispensing the nitrogen gas into the solution and the other, ending just below the stopper, served as the outlet for the gas. The probe of a dissolved oxygen meter (DO_2 Meter, Model 9071, Jenway, U.K.) was introduced through the third hole [figure 4.4]. In this experiment, the dissolved oxygen meter was used to measure oxygen concentration in the water. High purity oxygen free nitrogen gas was bubbled with a constant flow rate and the readings of the oxygen meter were noted at different times. A stopwatch was used for timing and a gas flow rate meter used to measure the flow rate of oxygen free nitrogen. A magnetic stirrer was used so that a uniform reading was obtained from the DO_2 meter.

Figure 4.5a shows the oxygen elimination time with a constant flow rate of 1000 cc/min for 2000ml, 1500 ml, 1000 ml, and 500 ml of deionised water. Figure 4.5b shows the oxygen elimination for a constant flow rate of 800 ml/min for 2000ml, 1000 ml, and 500 ml of deionised water. All curves of both figures have the form of an exponential decay. So, oxygen elimination time down to a certain level can be estimated using following equation:

$$[O_2](t) = [O_2]_i e^{-t/T_{e\lim}} \quad [4.17]$$

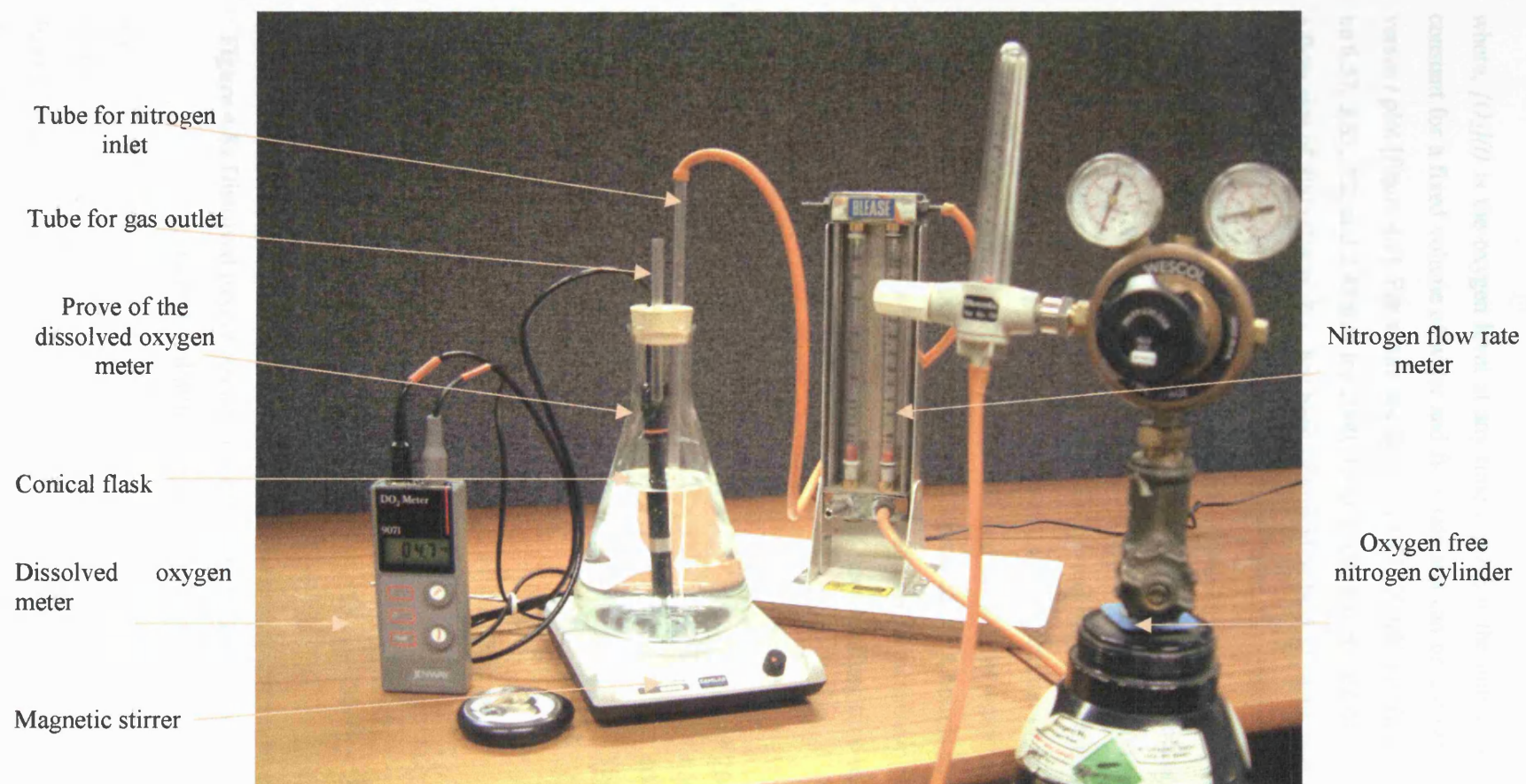


Figure 4.4 Experimental set up for measuring oxygen elimination time.

where, $[O_2](t)$ is the oxygen level at any time t , $[O_2]_i$ is the initial oxygen level, T_{elim} is a constant for a fixed volume of water and flow rate and can be estimate from $\ln[O_2(t)/(O_2)_i]$ versus t plot [figure 4.6]. For a constant flow rate of 1000 ml/min, T_{elim} has been estimated to be 6.57, 3.85, 3.2, and 2.45 min for 2000, 1500, 1000, and 500 ml of water respectively. For a flow rate of 800 ml/min, T_{elim} has been estimated to be 8.31, 4.13, and 3.03 min for 2000, 1000, and 500 ml of water respectively. Using these T_{elim} values in equation 4.14, it is possible to estimate the oxygen elimination time down to any level. For a constant flow rate of 1000 ml/min the oxygen elimination (1%) time has been estimated as 30, 18, 15 and 11 minute for 2000, 1500, 1000, and 500 ml. For the flow rate of 800 ml/min, the oxygen elimination (1%) time has been estimated as 38, 19 and 14 minute for 2000, 1000, and 500 ml of water. Time for oxygen elimination down to 0.1% require 45 min for 2 litres water with nitrogen flow rate of 1000 ml/min and 57 min for 2 litres water with flow rate of 800 ml/min. This study shows that to prepare up to 2 litres of gel, 1 hour is sufficient to eliminate oxygen down to 0.1% and a higher water volume requires an increase in the time required for oxygen elimination. In subsequent experiments, a 1-hour bubbling time was adopted.

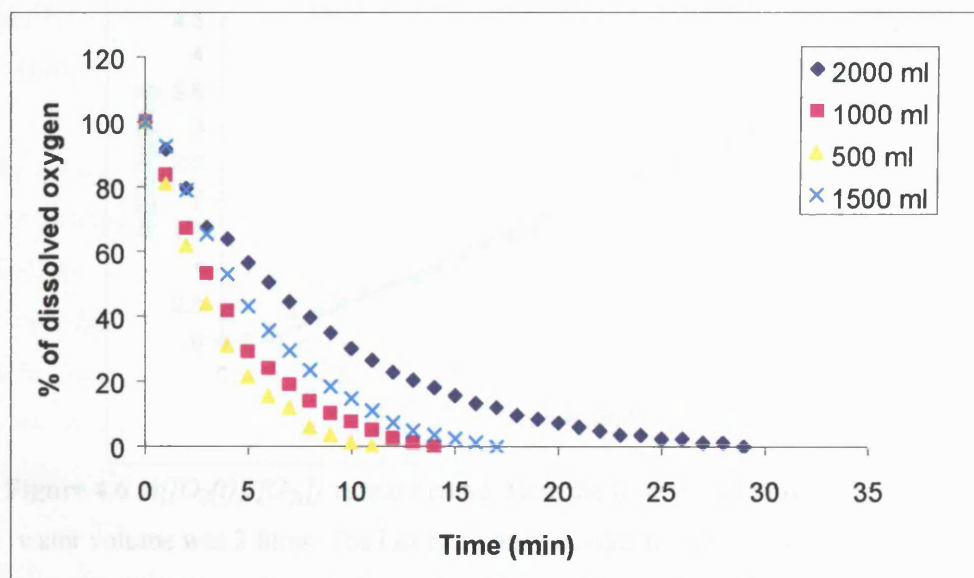


Figure 4.5a Dissolved oxygen versus time curve. Here the flow rate of nitrogen was 1000 cc/min, and different volumes of gel are shown.

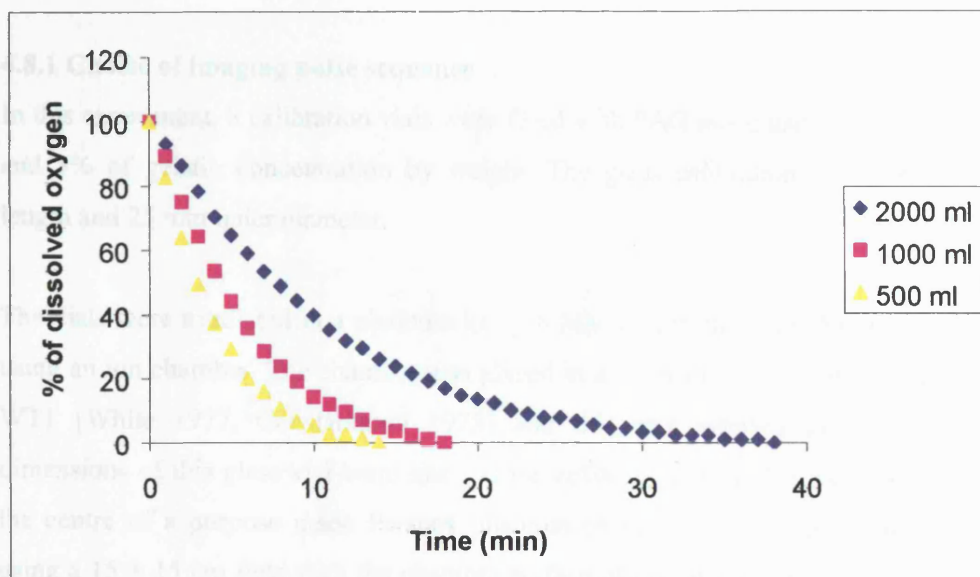


Figure 4.5b Dissolved oxygen versus time curve. Here the flow rate of nitrogen was 800 cc/min.

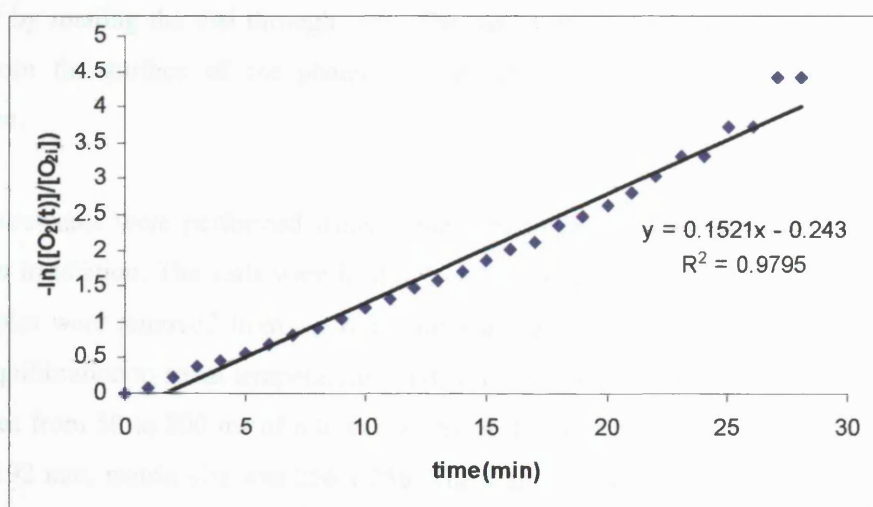


Figure 4.6 $\ln([O_2(t)]/[O_{2i}])$ versus t curve. Here the flow rate of nitrogen is 1000ml/min, and water volume was 2 litres. The last two points deviate from the straight line. Since the DO_2 meter is not sufficiently sensitive to detect small variations of oxygen concentration because it evaluates the O_2 concentration only to one decimal place of precision.

4.8 Optimisation of PAG

This section addresses the major properties of PAG gels. These include the choice of imaging pulse sequence, precision, method of calibration, response in low dose region, temperature dependences and energy dependence.

4.8.1 Choice of imaging pulse sequence

In this experiment, 8 calibration vials were filled with PAG made using 7% of total monomer and 5% of gelatin concentration by weight. The glass calibration vials were 100 mm in length and 25 mm outer diameter.

The vials were irradiated in a phantom using 6 MV x-rays, the beam having been calibrated using an ion chamber. The chamber was placed in a cylinder of water substitute epoxy resin, WT1 [White 1977, Constantinou 1978] and this was inserted into a glass vial. The dimensions of this glass vial were same as the calibration vials. The vial was then placed in the centre of a purpose made Perspex phantom (Figure 4.7). The phantom was irradiated using a 15×15 cm field with the phantom surface placed at a source to skin distance (SSD) of 95 cm. For all experiments, each set of vials was irradiated to absorbed doses of 0, 1, 2, 4, 6, 8, 10 and 12 Gy. In order to give uniform a dose and avoid dose gradients across the vials, the total dose was given in two equal parts with irradiations from opposite sides. This was achieved by rotating the vial through 180° . The maximum build up was observed at 1.5 cm ✓ depth from the surface of the phantom. The vials were stored in a refrigerator after irradiation.

R_2 measurements were performed using a Siemens Impact 1 T whole body scanner three days after irradiation. The vials were held in a polystyrene box during the scan [Figure 4.8]. Gel samples were removed from the refrigerator at least 24 hours prior to measurement, to ensure equilibration to room temperature. First, a multi-spin-echo sequence was used with 16 echo times from 50 to 800 ms of interval 50 ms. A TR of 3000 ms was used with a field of view of 192 mm, matrix size was 256×256 . The scan time was 12 minute 49 s. Secondly, a single spin-echo sequence was used with four separate echo times of 12, 400, ✓700 and 1000 ms. TR was 3064 ms, field of view was 192 mm, matrix size of 192×256 has been used. For each echo time, the scan took 9 minutes 52 s, so the total acquisition time was 39 minutes 48s.

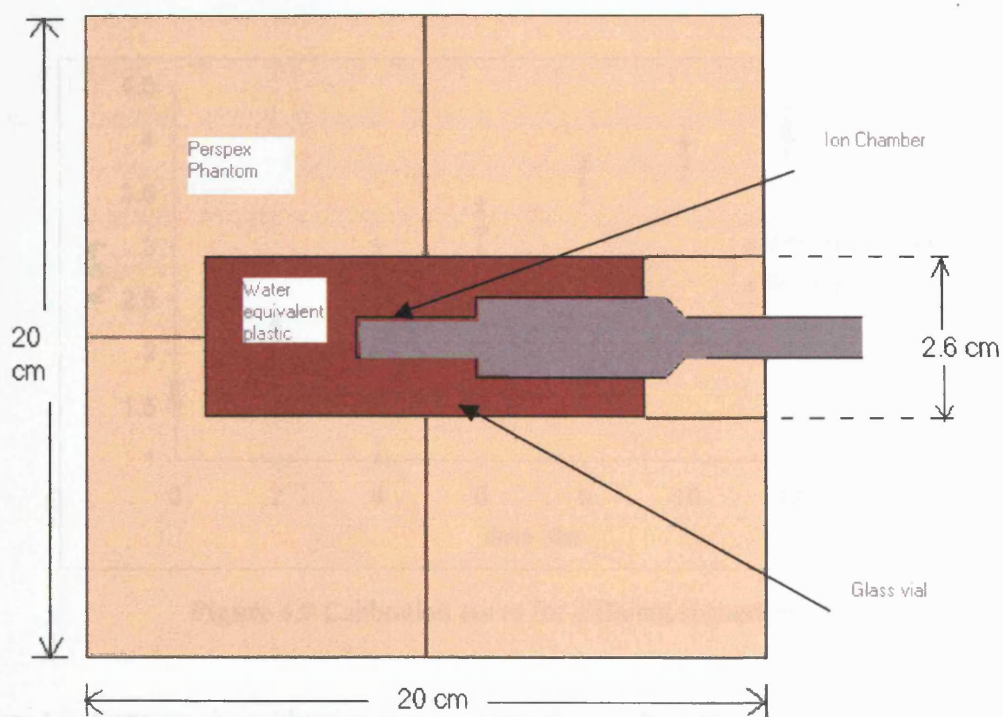


Figure 4.7 Cross-sectional view of set up for beam calibration.

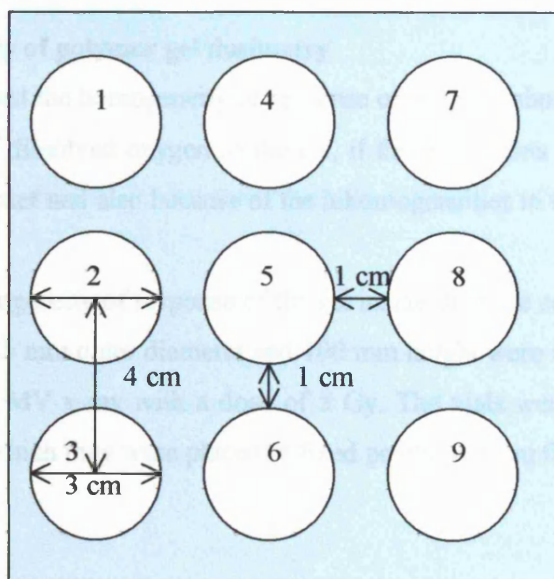


Figure 4.8 Position of the vials inside the holder where R_2 is measured.

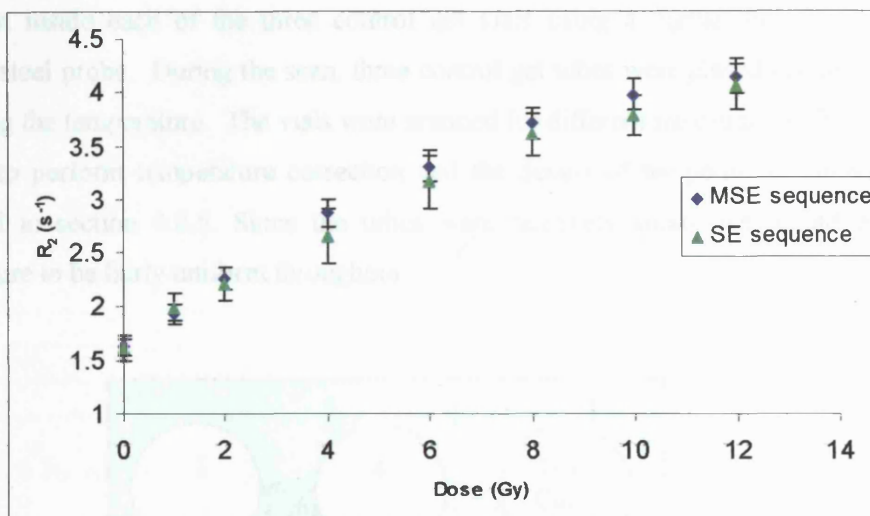


Figure 4.9 Calibration curve for different sequences.

Figure 4.9 illustrates the calibration curves obtained using both the multi-spin echo sequence and spin echo sequences. From the result it is evident that the R_2 measurement for multi-spin echo sequence and spin echo sequences are not statistically different ($P > 0.05$, t-test). No measurable difference except the scanning time was found between sequences.

4.8.2 Homogeneity of polymer gel dosimetry

It is important to test the homogeneity of response of the gel. Inhomogeneities may occur due to the presence of dissolved oxygen in the gel, if the ingredients of the gel are not properly dissolved in the water and also because of the inhomogeneities in the RF pulse amplitude.

To verify the homogeneity of response of the gel inside the knee coil, 6 cylindrical glass vials with dimensions 25 mm outer diameter and 100 mm height were filled with polymer gel and irradiated using 6 MV x-ray with a dose of 5 Gy. The vials were imaged in a polystyrene sample holder in which they were placed in fixed positions 1 cm from each other as shown in Figure 4.10.

In order to investigate position related errors, the same vials were imaged at different positions inside the knee coil. Before starting scanning, the tubes were marked and the position inside the coil was noted as in Figure 4.10. The vials were imaged six consecutive times in the rectangular polystyrene holder in which each tube was placed in each of six

different positions for the six different scans. The temperature was recorded at the time of each scan inside each of the three control gel vials using a digital thermometer with a stainless steel probe. During the scan, three control gel tubes were placed inside the coil for measuring the temperature. The vials were scanned for different temperatures from 9.5 °C to 27.4 °C to perform temperature correction and the details of temperature correction were described in section 4.8.5. Since the tubes were relatively small, we would expect the temperature to be fairly uniform throughout.

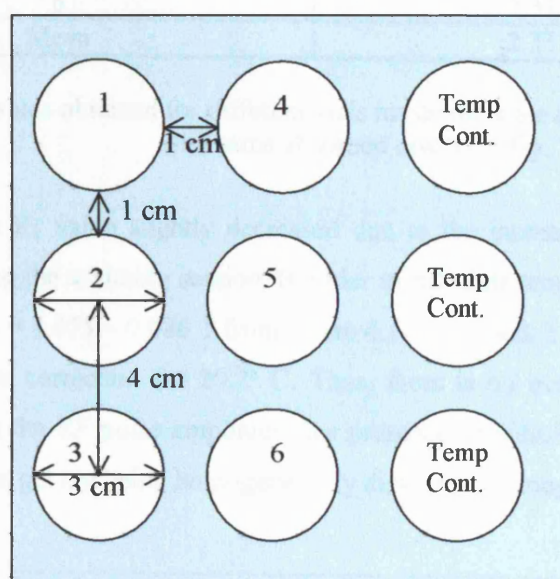


Figure 4.10: Position of the vials inside the knee coil. Distance between vials was 1 cm.

Table 4.1 shows the mean of three R_2 values measured from three slices (slice thickness was 3 mm and the gap between the slices was 1.5 mm) of a scan for each vial position in a rectangular polystyrene holders inside the knee coil. From the data, the mean R_2 value was $2.33 \pm 0.01 \text{ s}^{-1}$ for all vials.

Table 4.2 shows the result of R_2 measurements in the irradiated vials for the different positions inside the knee coil, where there was a small variation of R_2 from one position to another. However, this variation is due to temperature, not due to inhomogeneity of the RF

pulse amplitude. Inside the receiver coil the temperature of the vials slightly increased from one scan to the next (Table 4.3).

Tube position	Mean R_2 (s^{-1})
1	2.32 ± 0.01
2	2.33 ± 0.01
3	2.35 ± 0.00
4	2.32 ± 0.02
5	2.34 ± 0.03
6	2.31 ± 0.01
Mean	2.33 ± 0.01

Table 4.1 R_2 values obtained for different vials inside the knee coil. All vials were irradiated with same absorbed dose of 5 Gy.

As a result, the R_2 value slightly decreased due to the increase of temperature inside the image coil during the scanning session. In order to calculate temperature corrected R_2 values, the equation, $R_2 = 4.075 - 0.086.T$ from figure 4.11 was used. Table 4.4 shows the R_2 -values after temperature correction for 20.2° C. Thus, there is no evidence of any effects due to inhomogeneity in the RF pulse amplitude, the presence of dissolved oxygen in the gel or the ingredients of the gel not being homogeneously distributed throughout the gel.

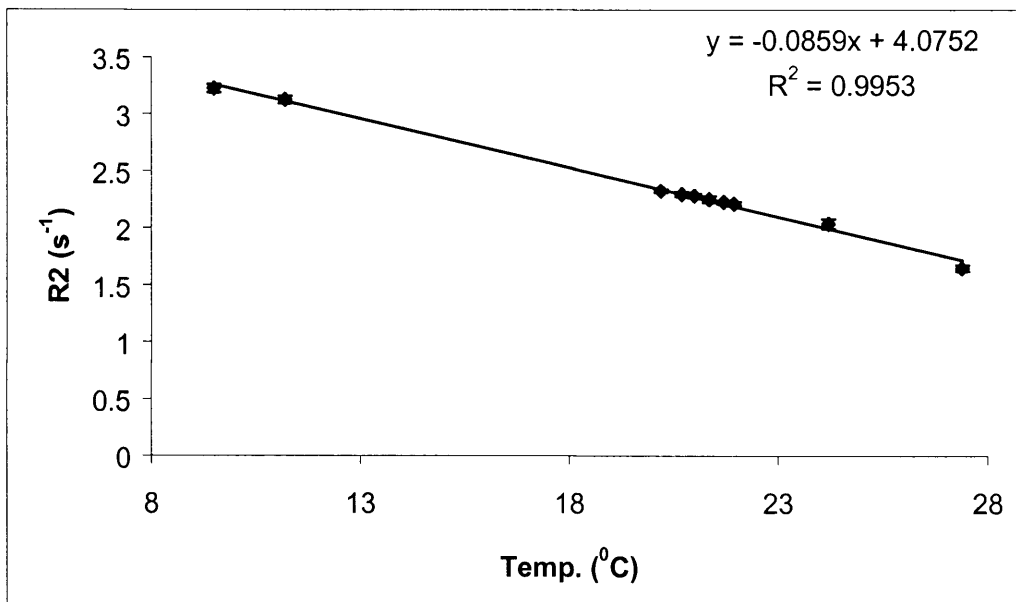


Figure 4.11 A graph of temperature versus R_2 .

Tube Position Tube No.	Position 1	Position 2	Position 3	Position 4	Position 5	Position 6	Mean
Tube No. 1	2.32 ± 0.01	2.30 ± 0.01	2.29 ± 0.05	2.28 ± 0.02	2.25 ± 0.03	2.23 ± 0.01	2.28 ± 0.03
Tube No. 2	2.22 ± 0.02	2.33 ± 0.02	2.29 ± 0.01	2.30 ± 0.04	2.27 ± 0.02	2.23 ± 0.01	2.27 ± 0.04
Tube No. 3	2.24 ± 0.02	2.22 ± 0.01	2.35 ± 0.01	2.33 ± 0.02	2.31 ± 0.04	2.28 ± 0.01	2.29 ± 0.05
Tube No. 4	2.22 ± 0.01	2.20 ± 0.03	2.19 ± 0.01	2.32 ± 0.01	2.28 ± 0.01	2.26 ± 0.04	2.25 ± 0.05
Tube No. 5	2.26 ± 0.04	2.24 ± 0.02	2.22 ± 0.02	2.23 ± 0.02	2.34 ± 0.03	2.30 ± 0.03	2.26 ± 0.05
Tube No 6	2.27 ± 0.02	2.27 ± 0.05	2.23 ± 0.02	2.22 ± 0.01	2.20 ± 0.02	2.31 ± 0.01	2.25 ± 0.04
Mean							2.267 ± 0.17

Table 4.2 R_2 values obtained at different positions inside the knee coil. All vials were irradiated with same dose of 5 Gy.

Scan No.	Temperature ($^{\circ}\text{C}$)
1	20.2 ± 0.3
2	20.7 ± 0.1
3	21.0 ± 0.1
4	21.4 ± 0.2
5	21.7 ± 0.1
6	22.0 ± 0.1

Table 4.3 Table of temperature at the time of scan.

Tube Position Tube No.	Position 1	Position 2	Position 3	Position 4	Position 5	Position 6	Mean
Tube No. 1	2.32 ± 0.01	2.32 ± 0.01	2.36 ± 0.05	2.38 ± 0.02	2.38 ± 0.03	2.38 ± 0.01	2.36 ± 0.03
Tube No. 2	2.37 ± 0.02	2.33 ± 0.02	2.33 ± 0.01	2.37 ± 0.04	2.37 ± 0.02	2.36 ± 0.01	2.36 ± 0.02
Tube No. 3	2.37 ± 0.02	2.37 ± 0.01	2.35 ± 0.01	2.37 ± 0.02	2.38 ± 0.04	2.38 ± 0.01	2.37 ± 0.01
Tube No. 4	2.32 ± 0.01	2.33 ± 0.03	2.34 ± 0.01	2.32 ± 0.01	2.32 ± 0.01	2.33 ± 0.04	2.33 ± 0.01
Tube No. 5	2.33 ± 0.04	2.34 ± 0.02	2.35 ± 0.02	2.38 ± 0.02	2.34 ± 0.03	2.34 ± 0.03	2.35 ± 0.02
Tube No 6	2.31 ± 0.02	2.34 ± 0.05	2.33 ± 0.02	2.35 ± 0.01	2.35 ± 0.02	2.31 ± 0.01	2.33 ± 0.02
Mean							2.35 ± 0.02

Table 4.4 R_2 values obtained at different positions inside the knee coil after temperature correction. All vials were irradiated with same dose of 5 Gy.

4.8.3 Comparison of different methods of calibration

Calibration is essential in order to measure both dose distributions and absolute dose. Different calibration methods were reported by several authors, these included (a) uniformly irradiating small gel tubes to different known doses [Maryanski et al 1994, Ibbott et al 1997, Baldock et al 1998], (b) using a single larger gel flask which is then irradiated at multiple locations with different known doses [Maryanski et al 1996, Farajollahi et al 2001] and (c) two test-tubes are irradiated with known doses and the calibration is then determined by fitting the depth dose measured in water, against the measured change in relaxivity with depth in the gel [Oldham et al 1998]. In this section, different calibration methods were performed and the advantages and disadvantages are discussed.

In order to investigate the different possible calibration methods (a & b), six vials were prepared. The dimensions of the vials were 100 mm length and 25 mm outer diameter. A Barex™ phantom (20 x 12 x 5 cm) was also prepared. All were filled with PAG from the same batch. The gels were irradiated on the same day as they were prepared. Six 4 x 4 cm regions were marked on both front and back surfaces of the Barex™ phantom corresponding to the radiation field. Prior to gel irradiation the dose to the centre of each area was determined using a calibrated PTW Unidos electrometer and NE 2581 ion chamber. Gels were irradiated using 6 MV x-rays with a radiation field of 4 x 4 cm and a source to surface

distance (SSD) of 95 cm. In order to give sufficient backscatter, 5 cm WT1 was placed behind the gel phantom. Gels were irradiated to absorbed doses of 0, 1, 2, 4, 6, and 8 Gy for both vials and phantom. MR images for both cases were made five days after irradiation and temperatures were recorded inside the gel during the scans.

A third calibration method, (c) [Oldham et al 1998b] was investigated and for this method, two identical cylindrical test tubes of gel, of outer diameter 25 mm and length 150 mm with a flat end were prepared. Gels were poured into each tube to just below the neck level and the tube firmly sealed with a rubber bung to prevent oxygen leakage. The vials were irradiated in a solid water phantom, which provided lateral scattering, and sufficient build-up for the photon beam using 6 MV x-rays with $5 \times 5 \text{ cm}^2$ irradiation field and SSD of 100 cm [Figure 4.12]. The beam was calibrated using an ion chamber. One tube was irradiated to 8 Gy at 5 cm depth from the surface of the water equivalent phantom, and the second to 5 Gy at 5 cm depth from the surface. Two test-tubes were required because for the 15 cm length tube, we had to ignore 6.75 cm of the length due to the bung and also because of oxygen contamination of the gel in the region a few cm from the top of the gel. Only 8.25 cm of the total length was used, and for 6 MV x-rays the dose from 6 cm to 14.25 cm depth (length 8.25 cm) reduced only around 62%. Measured central axis depth dose data from MRI images were compared with planning depth-dose data and corresponding R_2 values were measured. Another set of calibration vials was prepared from the same gel and irradiated uniformly to 0, 1, 2, 4, 6 and 8 Gy.

Figure 4.13 shows an R_2 image of the calibration phantom(b) with irradiated area of 0, 1, 2, 4, 6, and 8 Gy. Table 4.5 shows the different R_2 values for the calibration methods (a) and (b). Figure 4.14 shows the calibration curves that were obtained using the method of calibration a compared with the calibration method (b). The linear fit parameters of the calibration data for the methods (b) and a were $R_2 = 1.820 + 0.263D$ and $R_2 = 1.682 + 0.218D$ respectively, where D is the absorbed dose. It is clear from the result that the calibration method a gives a different slope from that of the method (b). Another curve for the method (b) is shown in Figure 4.14 after temperature correction and the linear fit parameters of this data were $R_2 = 1.805 + 0.256D$. Even after temperature correction, curves for both methods (a) and (b) still show significant differences.

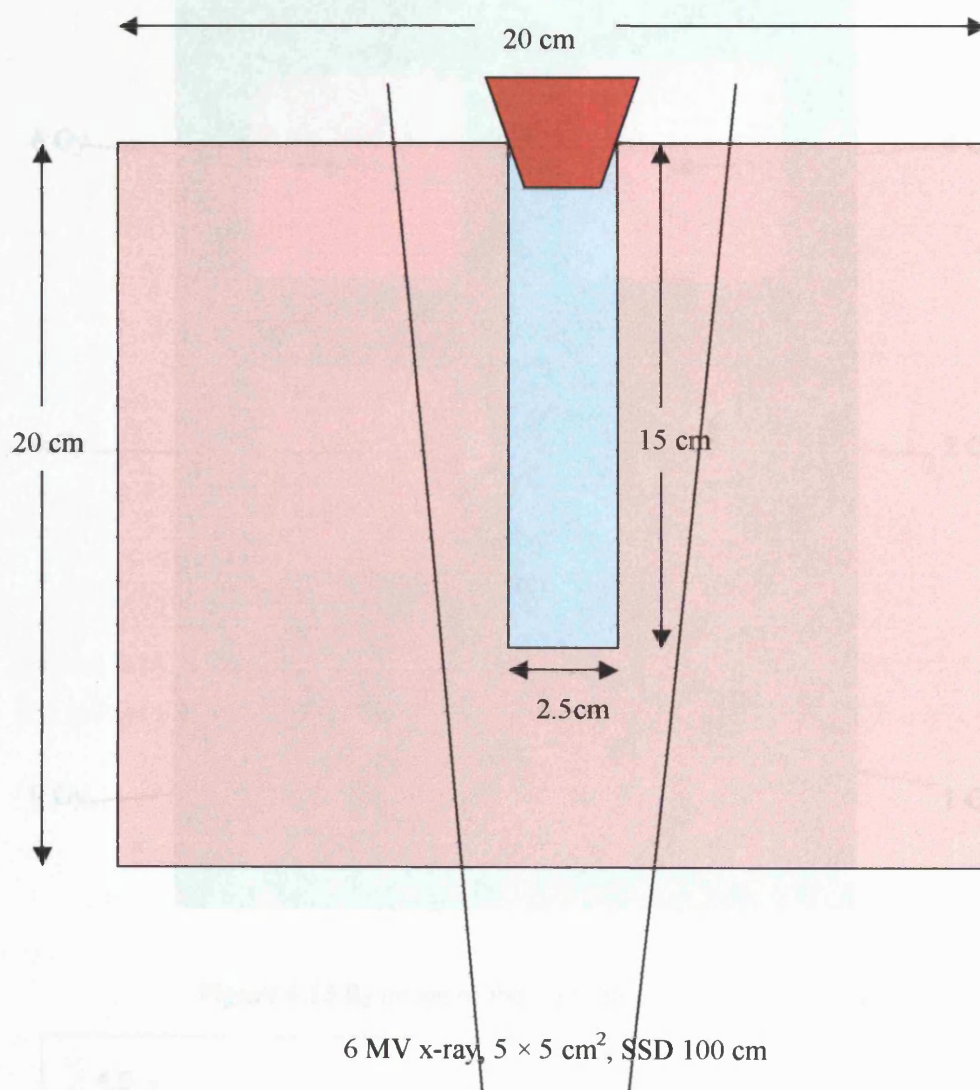


Figure 4.12 Illustration of Oldham's calibration (method c) set-up for irradiation.

Dose (Gy)	$R_2 \text{ (s}^{-1}\text{)}$ for method (b)	$R_2 \text{ (s}^{-1}\text{)}$ for method (a)	Difference (%)
0	1.759 ± 0.01	1.648 ± 0.01	6.74
1	2.056 ± 0.01	1.878 ± 0.01	9.48
2	2.346 ± 0.01	2.121 ± 0.01	10.61
4	2.971 ± 0.01	2.636 ± 0.01	12.71
6	3.527 ± 0.01	3.034 ± 0.01	16.25
8	3.776 ± 0.01	3.358 ± 0.01	12.45

Table 4.5 Difference in R_2 for the calibration method (a) and (b).

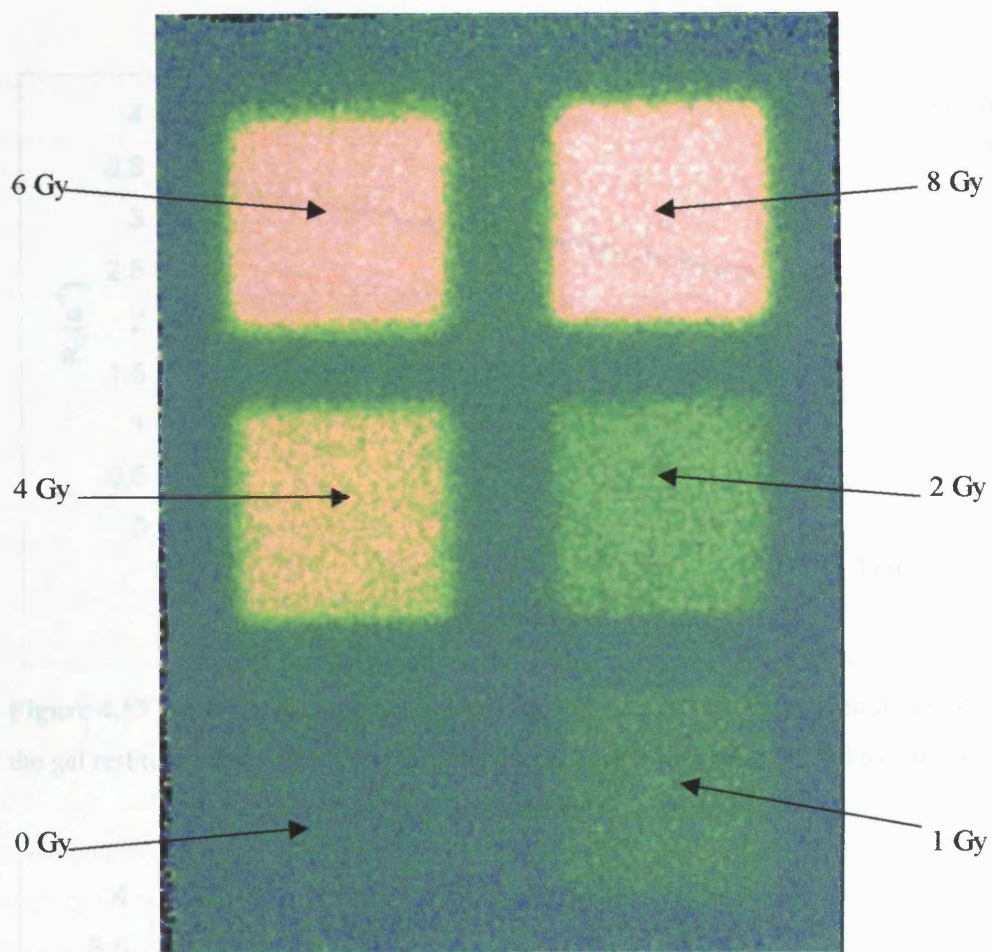


Figure 4.13 R_2 image of the calibration phantom (method b).

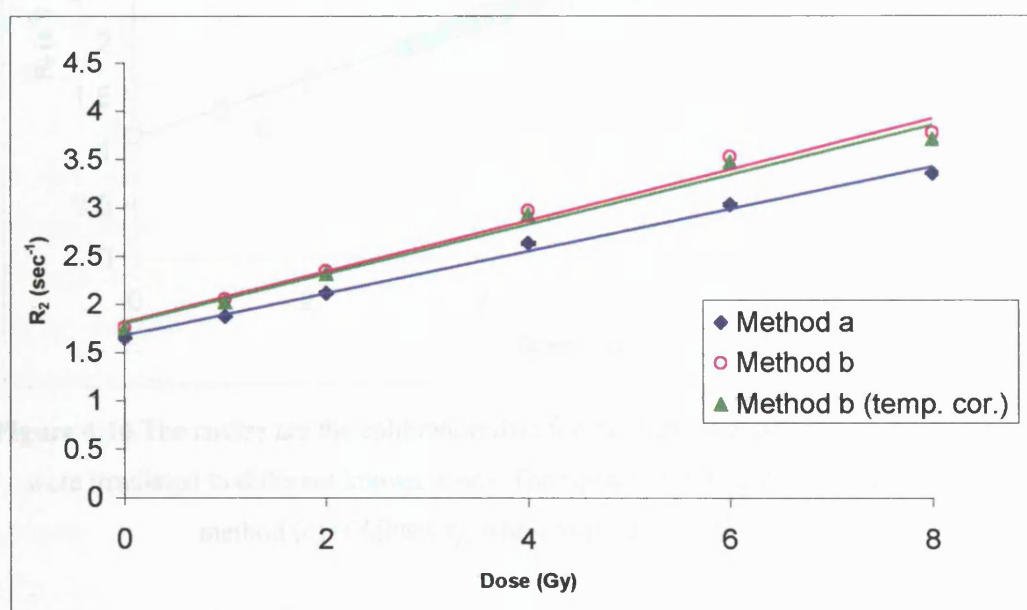


Figure 4.14 Comparison of different method of calibration

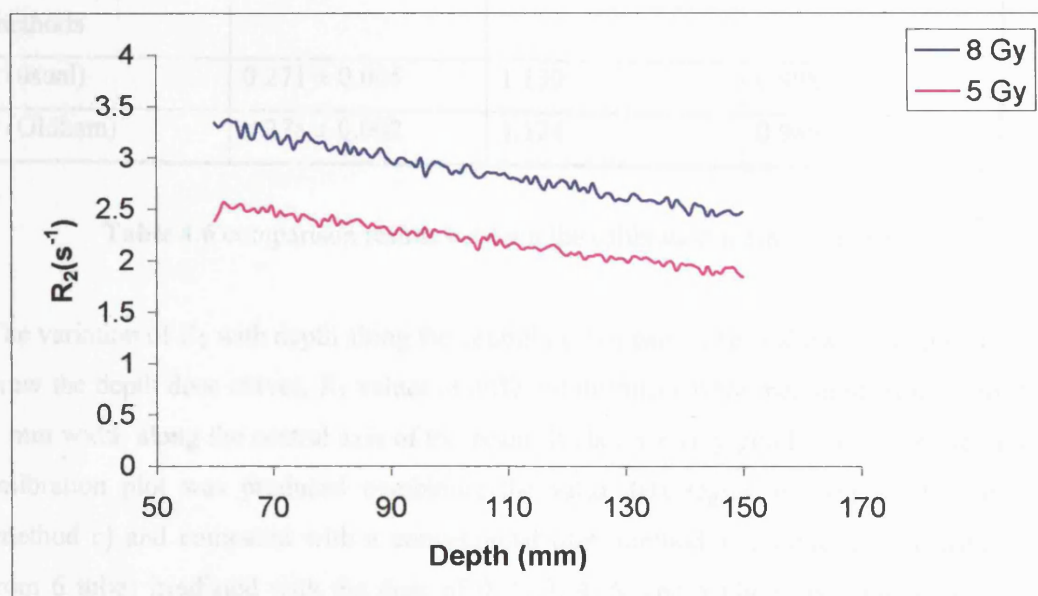


Figure 4.15 Depth- R_2 data measured from the MRI image along the central line of pixels of the gel test tubes from 60 mm to 150 mm depth. One tube was irradiated to a maximum of 8 Gy and another to 5 Gy.

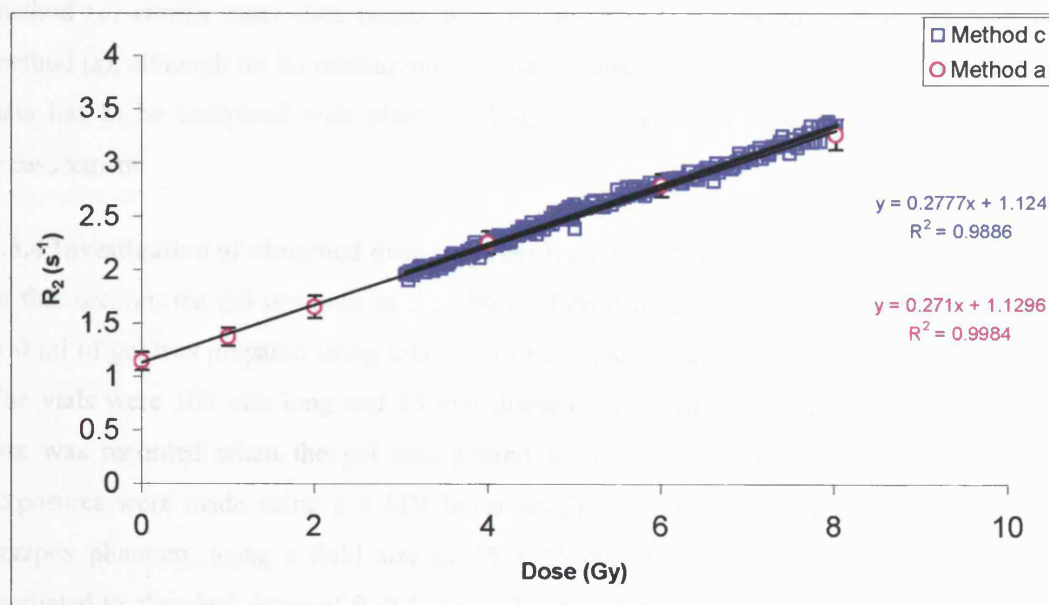


Figure 4.16 The circles are the calibration data for the method a, where six calibration tubes were irradiated to different known doses. The squares are the calibration data using the method (c) (Oldham's), where two tubes were irradiated.

Calibration methods	Slope ($s^{-1}Gy^{-1}$)	Intercept (s^{-1})	R^2
a (usual)	0.271 ± 0.005	1.130	0.998
c (Oldham)	0.278 ± 0.002	1.124	0.989

Table 4.6 comparison results between the calibration methods (a) and (c). ✓

The variation of R_2 with depth along the central axis of each tube is shown in Figure 4.15. To draw the depth dose curves, R_2 values at different distances were measured from a profile of 3 mm width along the central axis of the beam. It shows a very good signal to noise ratio. A calibration plot was produced combining the valid data region of both calibration vials (method c) and compared with a conventional plot (method a) produced from data obtain from 6 tubes irradiated with the dose of 0, 1, 2, 4, 6, and 8 Gy x-rays (Figure 4.16). The linear fit parameters of methods c and a were $R_2 = 1.124 + 0.278D$ ($R^2=0.989$) and $R_2 = 1.130 + 0.271D$ ($R^2=0.998$) respectively. From the experiment it is evident that the results were not statistically different ($P>0.05$, t-test). From Table 4.6 it can be seen that since the method (c) carries more data points than the method a, its standard error is lower than method (a), although for R_2 measurement using the method (c), the measured R_2 versus depth data has to be compared with planning data, which has been derived from ion chamber measurement.

4.8.4 Investigation of absorbed dose response from 0 to 2 Gy

In this section, the gel response in the absorbed dose range from 0-2 Gy was investigated. 400 ml of gel was prepared using total 7% of monomer concentration for 6 calibration vials. The vials were 100 mm long and 25 mm diameter. Oxygen concentration inside the glove box was recorded when the gel was poured from conical flask to the calibration vials. Exposures were made using a 6 MV linear accelerator. Irradiations were given inside the Perspex phantom, using a field size of 15×15 cm and SSD of 95 cm. The vials were irradiated to absorbed doses of 0, 0.4, 0.8, 1.2, 1.6 and 2.0 Gy, and scanning was performed ✓ using a Siemens Impact 1 T whole body scanner 3 days after irradiation. A multi-spin echo sequence with 16 TE values from 50 to 800 ms with 50 ms time interval and TR of 3000 ms was used.

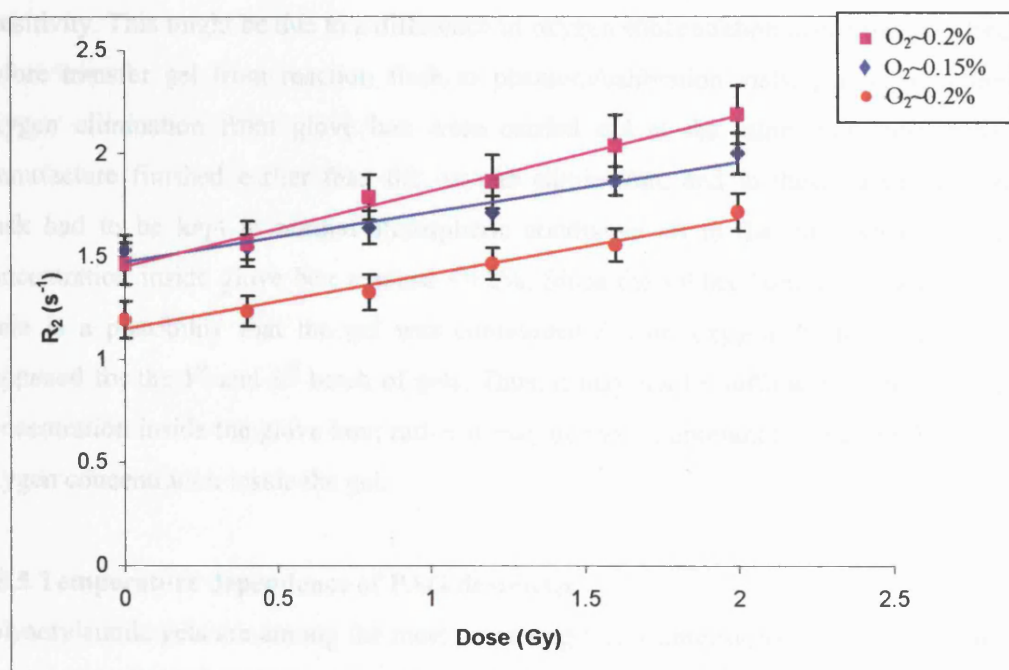


Figure 4.17 Linearity of the gel dose response from 0 to 2 Gy, where squares, diamonds, and circles indicate oxygen concentration of 0.2, 0.15, and 0.2 % inside the glove box at the time of pouring gel.

Oxygen concentration (%)	Slope (Gy ⁻¹ s ⁻¹)	Intercept (s ⁻¹)	R ²
0.15 (1 st batch)	0.241 ± 0.029	1.475 ± 0.035	0.946
0.20 (2 nd batch)	0.365 ± 0.019	1.451 ± 0.023	0.989
0.20 (3 rd batch)	0.266 ± 0.022	1.149 ± 0.026	0.974

Table 4.7 Gel sensitivity for the low dose region (0-2 Gy)

Figure 4.17 shows the R_2 versus dose curves where it can be seen that the response is linear within the lower dose region when the oxygen concentration in the glove box was $< 0.2\%$. Table 4.7 shows that the sensitivity of gel in the lower dose region does not depend on oxygen concentration inside the glove box. It was mentioned earlier that the sensitivity of the gel in the linear region depends on monomer concentration, photo polymerisation and also the dissolved oxygen concentration inside the gel. In this experiment all three batches of gels were made from same concentration of monomer although the results show different

sensitivity. This might be due to a difference in oxygen concentration inside the gel. Because before transfer gel from reaction flask to phantom/calibration vials, gel manufacture and oxygen elimination from glove box were carried out at the same time. Sometimes gel manufacture finished earlier than the oxygen elimination, and in these cases the reaction flask had to be kept in normal atmospheric conditions up to the time when the oxygen concentration inside glove box reached $<0.2\%$. Since the rubber bung is not a perfect seal, there is a possibility that the gel was contaminated with oxygen during that time. This happened for the 1st and 3rd batch of gels. Thus, it may not be sufficient to measure oxygen concentration inside the glove box; rather it may be more important to measure the dissolved oxygen concentration inside the gel.

4.8.5 Temperature dependence of PAG dosimeter

Polyacrylamide gels are among the most promising three-dimensional dose verification tools developed to date. However, the problem is that they are usually used to give relative dose distributions and the ability to measure absolute doses accurately has been the cause for much debate and large variations have been recorded (e.g. Farajollahi *et al.* 1999, Low *et al.* 1999, Cosgrove *et al.* 2000). It is possible that the size difference between the main phantom and calibration tubes is a contributory factor. Farajollahi *et al.* (2001) showed that the slope of the gel dose response was $0.24 \pm 0.01 \text{ s}^{-1} \text{ Gy}^{-1}$ for calibration vials, and $0.33 \pm 0.003 \text{ s}^{-1} \text{ Gy}^{-1}$ for a large phantom. In addition, variations in the manufacturing process (Oldham *et al.* 1998b) or of the thermal history of the samples (Salomons and Schreiner, 1999) may cause differences between calibration samples and phantoms. Another possible contributory factor is the temperature difference between the phantoms and calibration vials at the time of scanning, since R_2 is strongly dependent on the temperature at the time of measurement. McJury *et al.* (1999a) have commented on this effect inside the RF coil. It is usual to scan the irradiated phantom and calibration vials at the same time under the same physical conditions. In this case, the NMR evaluation of the phantom is usually done without a correction for temperature. However, there may be situations when this is not possible. when it becomes necessary to do temperature correction.

When the protons are placed in a strong external magnetic field, the dipole moments of the proton align with this magnetic field. Some of the protons align parallel with the direction of magnetic field, whereas slightly fewer protons align anti-parallel with the magnetic field. The difference between parallel and anti parallel spin depends on temperature and on the

magnetic field strength. The difference of the energy ultimately affects the signal-to-noise ratio (SNR), which is one aspect of image for image quality. The population difference can be increased by cooling the object and also by increasing the field strength; the former is easier to do. However if the NMR evaluation of phantom is performed at a lower temperature, then it is also necessary to perform a temperature correction.

The aim of this study is to investigate temperature effects during the NMR evaluation and to be able to produce a temperature corrected MRI dose image using a non-linear least square-fitting program. Dose distributions for three different temperatures and doses were obtained and compared with the given dose.

The temperature dependence of gel has been studied by several authors [Maryanski et al 1994, 1995b, 1997a, DeDeene et al 1998, Spevacek et al 2001]. Maryanski et al [1994] showed that the temperature at the time of irradiation does not affect the dose response but at the time of scanning it has a significant effect, for example the dose response is $0.25 \text{ s}^{-1}\text{Gy}^{-1}$ at room temperature and $0.44 \text{ s}^{-1}\text{Gy}^{-1}$ at 0°C . In another study Maryanski et al [1995b] showed that dose sensitivity at 5°C is $0.52 \text{ s}^{-1}\text{Gy}^{-1}$ and it decreases to $0.15 \text{ s}^{-1}\text{Gy}^{-1}$ at 40°C , i.e. decreasing by more than $0.01 \text{ s}^{-1}\text{Gy}^{-1}$ per degree Celsius [Maryanski et al 1995b, 1997a]. De Deene et al [1998] et al showed that both dose response and background varied linearly with temperature. They found the dose response decreased by $7.6 \times 10^{-3} \text{ s}^{-1} \text{Gy}^{-1}$ per $^\circ\text{C}$. Spevacek et al in 2001 proposed a method to correct the measured NMR R_2 dose response for different temperatures.

4.8.5.1 Materials and methods

Gels were made using 5% gelatin, 3% acrylamide and 3% bis acrylamide. Seven calibration tubes and a rectangular phantom ($20 \times 12 \times 5 \text{ cm}$) were prepared for this investigation. The calibration vials were irradiated using 6 MV x-rays from a linear accelerator (Elekta SLi) to doses of 2, 4, 6, and 8 Gy and three left unexposed. One unexposed vial was used to measure background (0 Gy) and the other two unexposed vials were used to measure temperature inside the MRI scanner. All calibration vials were irradiated inside a Perspex phantom using a field size of $15 \times 15 \text{ cm}$ and SSD of 95 cm. A rectangular phantom was irradiated using 300 kVp x-rays from a Pantak DXT-300 orthovoltage x-ray machine (Pantak Inc., Connecticut, USA) with a 0.80 mm Sn, 0.25 mm Cu and 1.5 mm Al filters. An absorbed dose of 8 Gy with a $10 \times 10 \text{ cm}$ applicator and 50 cm SSD were used in this experiment.

Evaluation of the dosimeters was performed 3 to 5 days after irradiation using an Impact 1 Tesla whole body scanner (Siemens, Germany) with a body coil transmitter/ knee coil receiver. A multi spin echo sequence was used. The echo time was 50 to 800 ms with an echo spacing time 50 ms and the repetition time was 3000 ms. The field of view was 192 mm, in-plane resolution 0.75 mm and the slice thickness was 3 mm. For each scan, the temperature in the gel was recorded at the beginning and at the end of the scan using a digital thermometer with a stainless steel probe.

R_2 images were produced using equation (4.14) using a non-linear least squares fitting program for different temperatures as previously described in section 4.6.

4.8.5.2 Results

Dose response curves for different temperatures are shown in figure 4.18. They show that the response was different for different temperatures, as expected. The figure shows that background R_2 also varied with temperature. The variation of sensitivity and background R_2 with temperature is shown in Table 4.8. Temperature dependent R_2 values for different dose levels are shown in figure 4.19. It can be seen that there is a linear relation between R_2 and temperature and response is different for different dose levels. The variation of R_2 with temperature is shown in table 4.9. The temperature dependence of both sensitivity and background obtained from the R_2 -versus-dose curves for different temperatures are shown in figure 4.20 and figure 4.21; both curves were found to linear. The dose sensitivity decreases $0.011 \text{ s}^{-1} \text{ Gy}^{-1} \text{ }^\circ\text{C}^{-1}$ and background decreases by $0.024 \text{ s}^{-1} \text{ }^\circ\text{C}^{-1}$. Temperature corrected dose images were produced using the following formulation:

On the basis of figure 4.18 the following general expression for R_2 can be written

$$R_2(T) = R_{2b}(T) + \rho(T).D \quad [4.18]$$

Where R_{2b} is the background R_2 , ρ is the dose sensitivity, D is the absorbed dose, and T is the temperature at the time of scanning. $\rho(T)$ and $R_{2b}(T)$ Can be obtained from figure 4.20 and 4.21:

$$\rho(T) = \rho_b + \alpha.T \quad [4.19]$$

$$R_{2b}(T) = R_{2bb} + \beta.T \quad [4.20]$$

where α is the slope of the dose sensitivity vs. temperature curve, ρ_b is the intercept of the same curve, and β is the slope of the background R_2 vs. temperature curve and R_{2bb} is the intercept of the same curve. Then by substituting Eq. [4.19] and Eq. [4.20] in Eq. [4.18], we can estimate R_2 for any temperature:

$$R_2(T) = R_{2bb} + \beta.T + (\rho_b + \alpha.T).D \quad [4.21]$$

Using Eq. [4.21], Eq.[4.14] can be written as

$$S = S_0 e^{-TE \cdot \{R_{2bb} + \beta.T + (\rho_b + \alpha.T).D\}} \quad [4.22]$$

Temperature corrected dose images were produced using a non-linear least squares fitting program based on equation [4.22].

Three temperature corrected dose images were produced for three different temperatures and compared with given dose [table 4.10]. The result showed good agreement between measured and given dose.

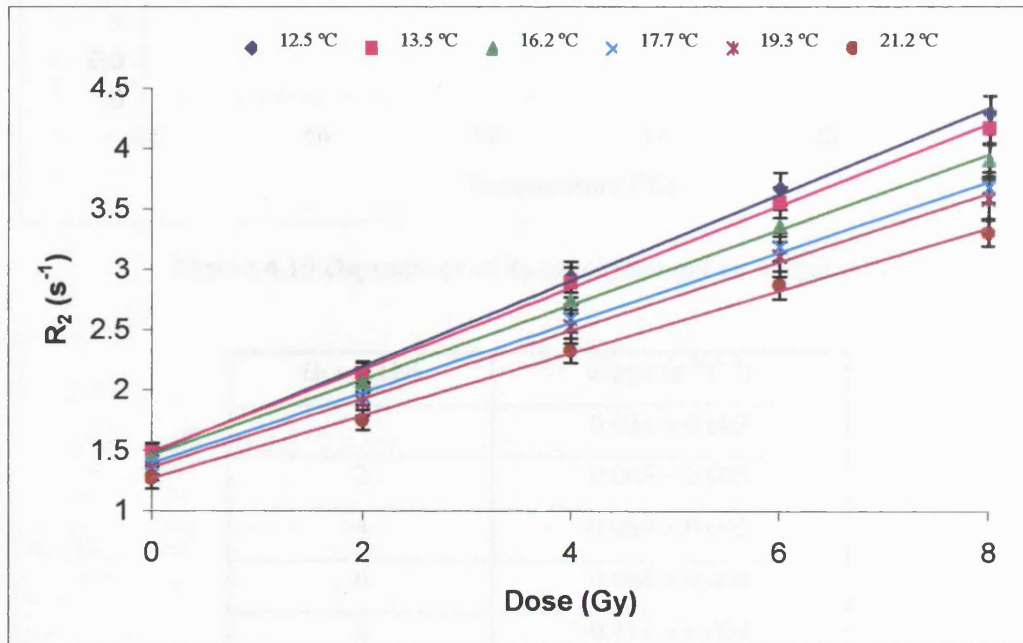


Figure 4.18 Dependence of R_2 on absorbed dose for different temperatures at the time of MR evaluation.

Temperature (°C)	Dose sensitivity (slope) ($\text{s}^{-1}\text{Gy}^{-1}$)	Background R_2 (intercept) (s^{-1})
12.5	0.357 ± 0.008	1.48 ± 0.04
13.5	0.339 ± 0.006	1.49 ± 0.03
16.2	0.311 ± 0.007	1.46 ± 0.03
17.7	0.291 ± 0.007	1.40 ± 0.04
19.3	0.283 ± 0.007	1.36 ± 0.04
21.2	0.259 ± 0.007	1.27 ± 0.03

Table 4.8 Variation of the polymer gel sensitivity and background with temperature.

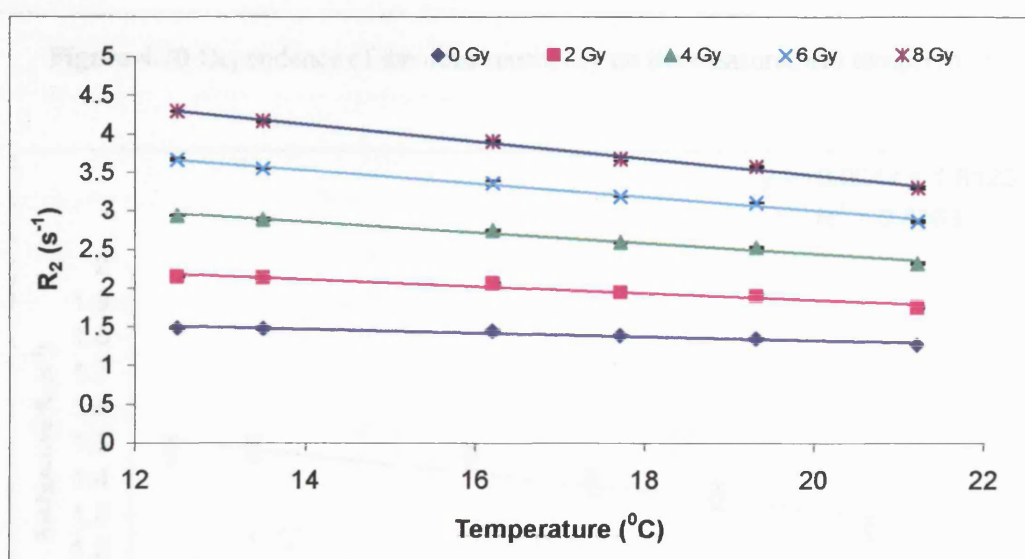


Figure 4.19 Dependence of R_2 of polymer gel on temperature

Dose (Gy)	Slope ($\text{s}^{-1}\text{°C}^{-1}$)
0	0.024 ± 0.003
2	0.045 ± 0.005
4	0.069 ± 0.005
6	0.088 ± 0.004
8	0.111 ± 0.004

Table 4.9 Variation of R_2 response with temperature for different dose levels.

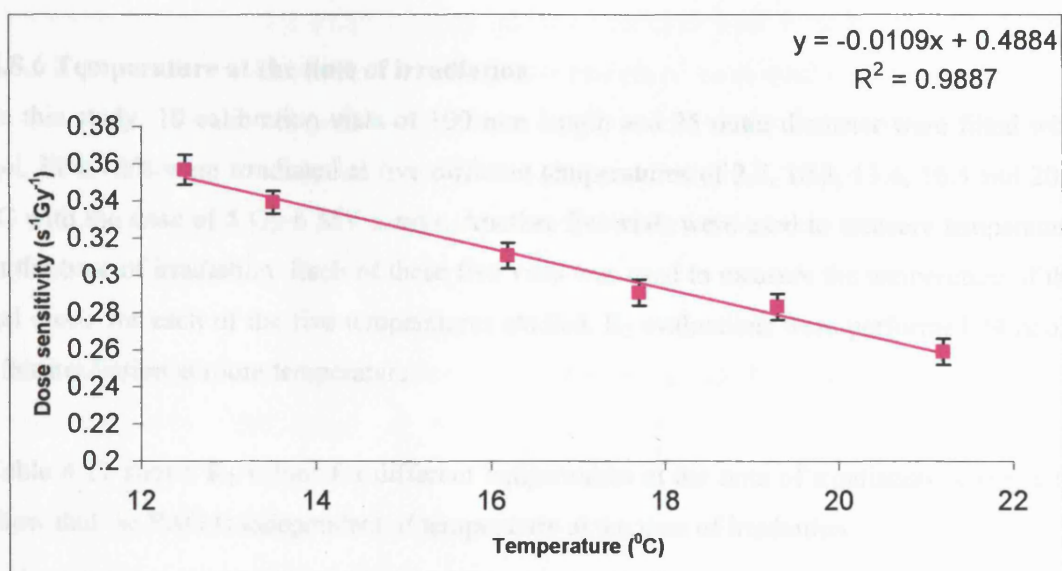


Figure 4.20 Dependence of the dose sensitivity on the measurement temperature.

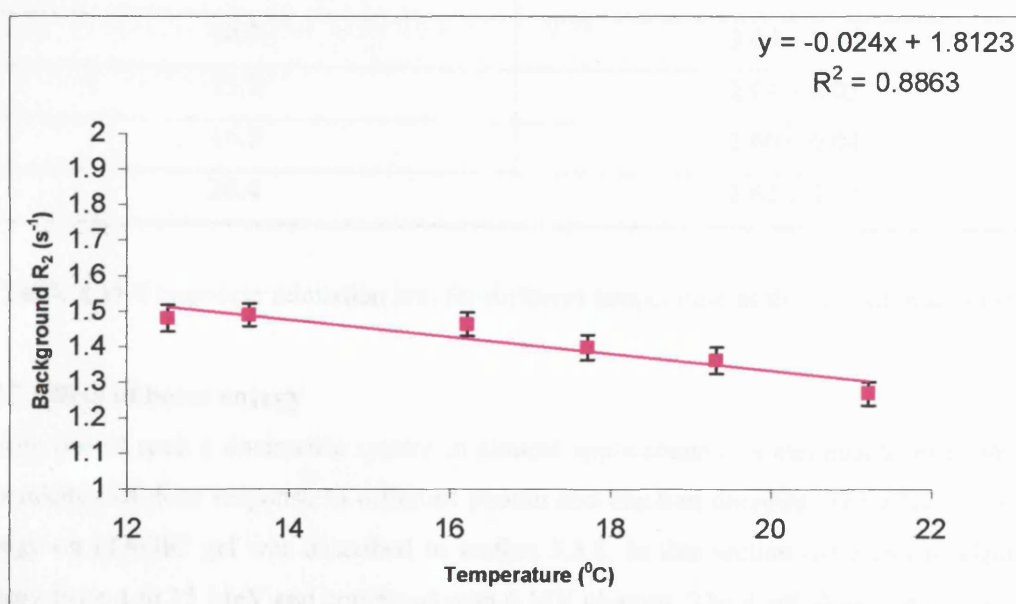


Figure 4.21 Dependence of the background R_2 on temperature.

Temperature (°C)	Given dose (Gy)	Measured dose (Gy)
16.2	8.0	8.1 ± 0.2
19.0	8.0	8.4 ± 0.2
21.1	8.0	8.3 ± 0.3

Table 4.10 Comparison of dose measurement at three different temperatures.

4.8.6 Temperature at the time of irradiation

In this study, 10 calibration vials of 100 mm length and 25 outer diameter were filled with gel. Five vials were irradiated at five different temperatures of 2.7, 10.3, 13.6, 16.5 and 20.4 °C with the dose of 5 Gy 6 MV x-rays. Another five vials were used to measure temperature at the time of irradiation. Each of these five vials was used to measure the temperature of the gel – one for each of the five temperatures studied. R_2 evaluations were performed 24 hours after irradiation at room temperature.

Table 4.11 shows R_2 values for different temperatures at the time of irradiation. The results show that the PAG is independent of temperature at the time of irradiation.

Temperature (°C)	R_2 (s ⁻¹)
2.7	2.62 ± 0.03
10.3	2.64 ± 0.04
13.3	2.64 ± 0.03
16.5	2.60 ± 0.04
20.4	2.62 ± 0.03

Table 4.11 Transverse relaxation rate for different temperature at the time of irradiation.

4.8.7 Effect of beam energy

Before use of such a dosimetric system in clinical applications it is essential to evaluate the dependency of dose response to different photon and electron energies. The effect of beam energy on MAGIC gel was described in section 5.3.8. In this section the effect of electron energy from 4 to 15 MeV and compared with 6 MV photons. The depth dose curves for 4, 6, 8, 10 and 12 MeV electron energies were investigated. Details of the experimental procedure are described in section 5.3.9.

For this study a set of 21 vials were prepared from a batch of gel and irradiated using 4, 8, 12 and 15 MeV electrons and 6 MV photon with doses from 0 to 8 Gy 4 hours after manufacture. Doses above 6 Gy were excluded because there was evidence of saturation of the polymer production (figure 4.22). For the depth dose measurement, 5 vials (two of them were 150 mm length and 25 mm outer diameter and the rests were 100 mm length and 25

mm outer diameter) were prepared with gel and irradiated with 4, 6, 8, 10, and 12 MeV electrons. Details of the irradiation set-up and procedure were described in section 5.3.8. Evaluation of the gel was performed 2 days after irradiation. The multi-echo sequence was used with a TR of 3000 ms and TE was 50 to 800 ms with an echo spacing of 50 ms. The field-of-view was 192 mm and matrix size was 256×256 . In plane resolution was 0.75 mm with slice thickness of 5 mm.

Calibration curves were obtained for each electron energy as shown in figure 4.23 with r^2 better than 0.99. The slopes of these curves were 0.40 ± 0.01 , 0.40 ± 0.01 , 0.40 ± 0.01 , 0.40 ± 0.02 , and 0.40 ± 0.01 for 4, 8, 12, 15 MeV electrons and 6 MV photons respectively. Figure 4.24 shows the slope of the dose response curve (0 – 6 Gy) versus electron energy, and slope of this plot was $0.00 \pm 0.001 \text{ s}^{-1} \text{ Gy}^{-1} \text{ MeV}^{-1}$. This indicates that the dose response of PAG gel is largely energy independent at least up to 6 Gy absorbed dose. The depth dose curve for electron energies of 4, 6, 8, 10, and 12 MeV are shown in figure 4.25. Table 4.12 shows the measured electron energies and compares it with the electron energies measured using ionisation chamber.

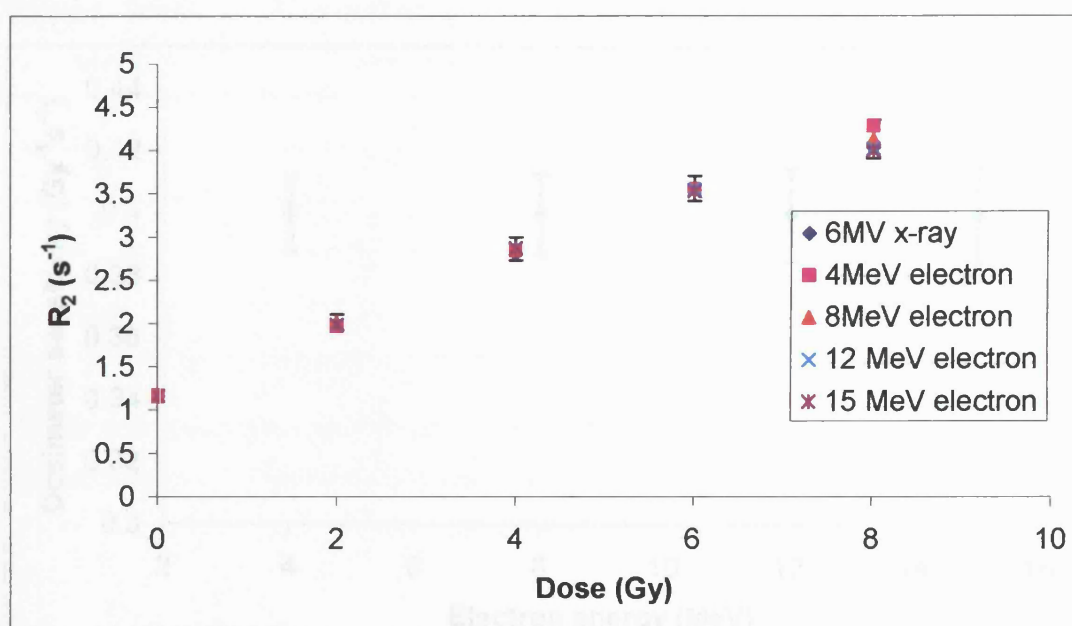


Figure 4.22 R_2 response to absorbed dose up to 8 Gy for electron energies of 4, 8, 12, and 15 MeV, compared with 6 MV x-rays.

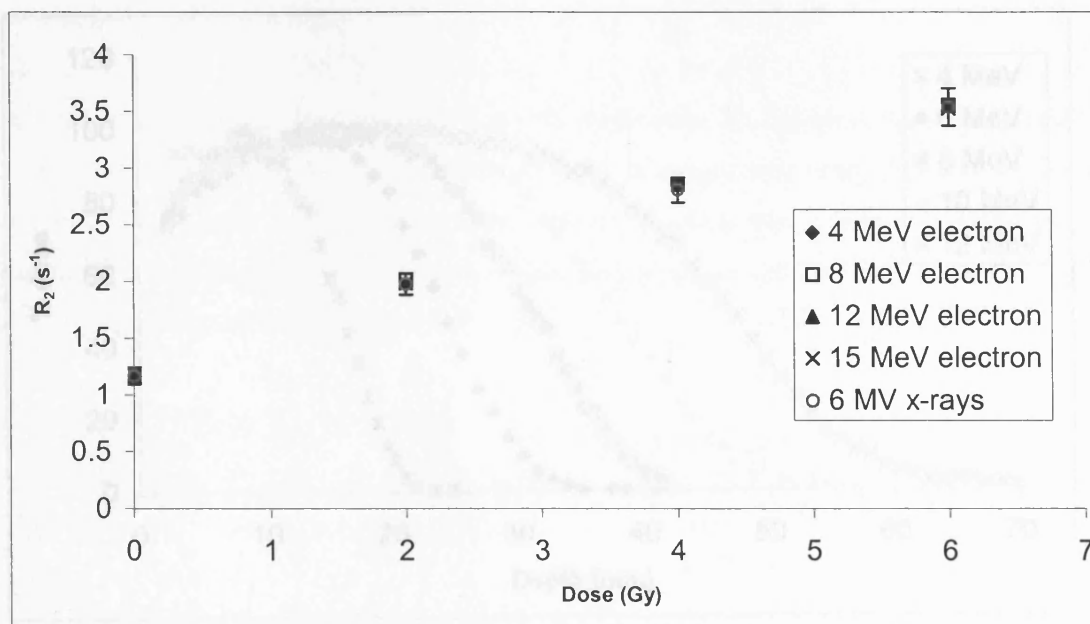


Figure 4.23 R_2 response to absorbed dose up to 6 Gy for electron energies of 4, 8, 12, and 15 MeV, compared with 6 MV x-rays.

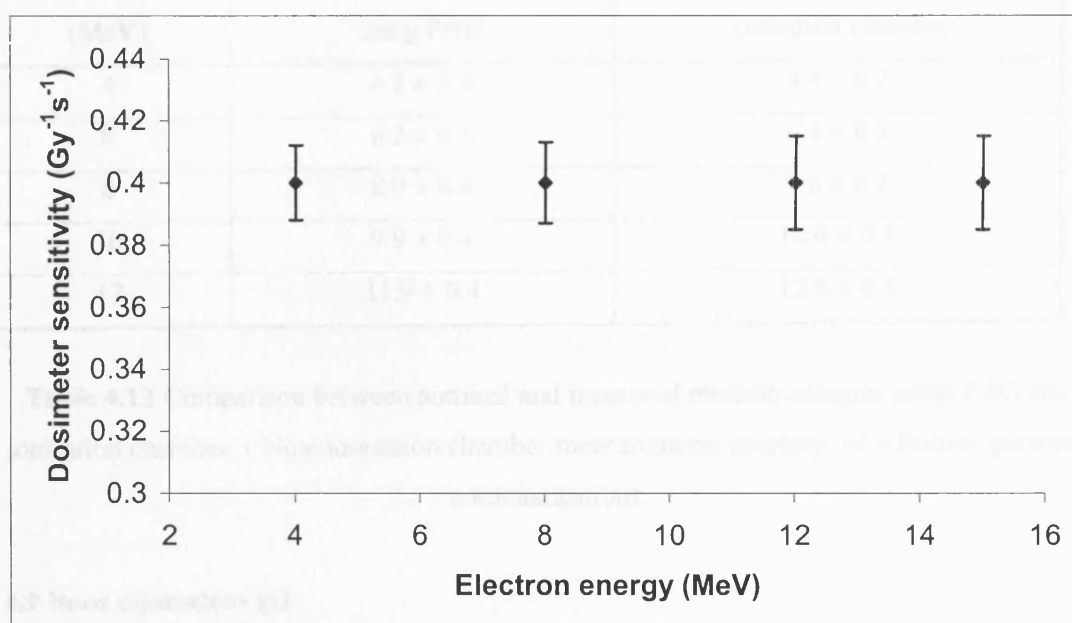


Figure 4.24 Dependence of PAG gel dosimeter sensitivity (up to 6 Gy) on electron energy in the centre of the glass vessel filled by PAG gel. Slope is $0.00 \pm 0.001 \text{ s}^{-1} \text{ Gy}^{-1} \text{ MeV}^{-1}$, with errors estimated using propagation of errors for individual measurements.

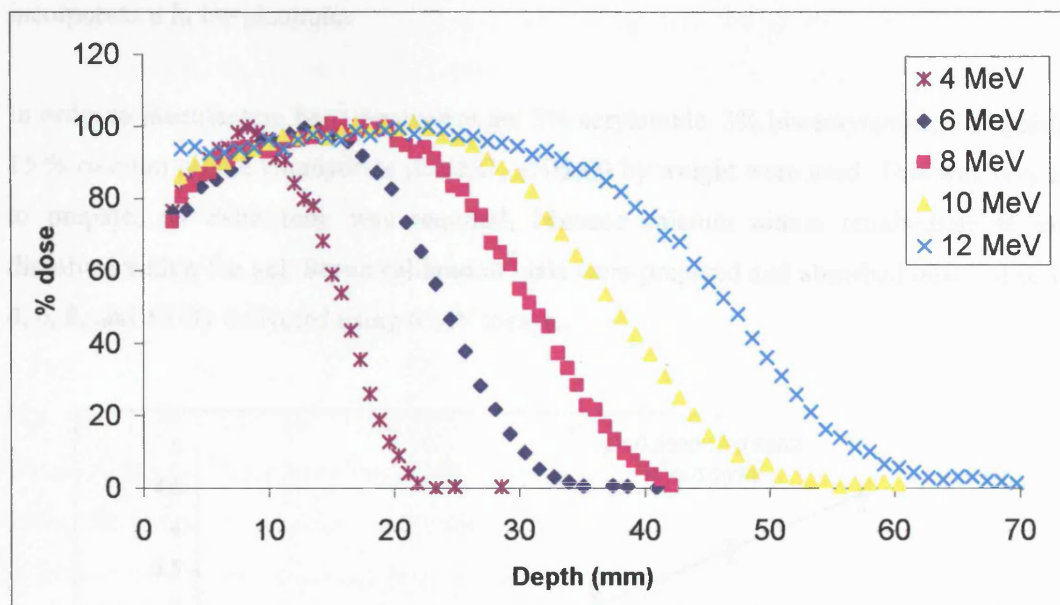


Figure 4.25 Depth dose curves for different electron energies.

Nominal Energy (MeV)	Measured energy (MeV) using PAG	Measured energy (MeV) using an ionisation chamber
4	4.2 ± 0.3	4.4 ± 0.2
6	6.2 ± 0.4	6.4 ± 0.2
8	8.0 ± 0.4	8.6 ± 0.2
10	9.9 ± 0.4	10.6 ± 0.3
12	11.9 ± 0.4	12.6 ± 0.3

Table 4.12 Comparison between nominal and measured electron energies using PAG and ionisation chamber. (Note ionisation chamber measurements courtesy of S Bolton: personal communication).

4.9 Bone equivalent gel

The effective atomic number of bone is greater than that of soft tissue, and its density, depending upon whether the bone is spongy or compact, is in the range $1.2\text{--}1.8\text{ g/cm}^3$ [Mould 1981]. Consequently, the presence of bone will cause a greater reduction in dose to the soft tissue beyond the bone, compared to the situation when no bone is present. For truly

anthropomorphic phantoms, it is desirable to be able to make bone equivalent gel and incorporate it in the phantom.

In order to manufacture bone-equivalent gel 3% acrylamide, 3% bis-acrylamide, 7% gelatine, 15 % calcium nitrate tetrahydrate ($\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$) by weight were used. This was very easy to prepare, no extra time was required, because calcium nitrate tetrahydrate is easily dissolved within the gel. Seven calibration vials were prepared and absorbed doses of 0, 1, 2, 4, 6, 8, and 10 Gy delivered using 6 MV x-rays.

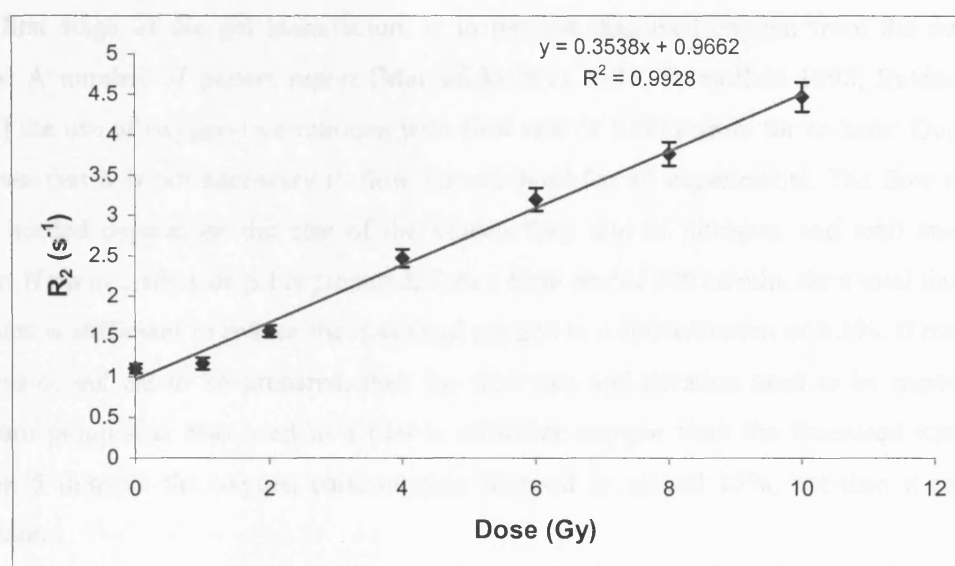


Figure 4.26 Calibration curve for bone gel.

Figure 4.26 shows the calibration curve for bone equivalent gel. It can be seen that dose response is linear up to 10 Gy. In this experiment, the density achieved was 1.2 gm/cm^3 . Another batch of gel was made with 1.4 gm/cm^3 density; however it did not remain solid at room temperature. This gel was irradiated at 0°C and the irradiated area appeared well defined and no diffusion was found. However after increasing the temperature, the gel became liquid.

4.10 Discussion

Polyacrylamide gels are among the most promising three-dimensional dose verification tools developed to date. In the gel formulation, acrylamide monomer and N, N' methylene-bis-acrylamide (bis) cross-linker are infused in a gelatin matrix. The principle of use is based on the radiation-induced polymerisation and cross-linking of these acrylic monomers

[Maryanski et al 1997a]. In recent years, an ever increasing number of articles have been published on both the fundamental properties and applications of PAG gel. However, until now, PAG gel dosimeters have not been widely used in the clinic. One of the reasons is that they are difficult to manufacture, since polymerisation in polymer gel is inhibited by oxygen, a fact which has already been reported by several authors e.g. Hoecker and Watking [1958] and Makhlis [1975]. Therefore in order to achieve polymerisation it is necessary to remove any oxygen from the gel. Nitrogen or nitrous oxide gases have been used to deoxygenate the polymer gels.

The first stage of the gel manufacture is to remove dissolved oxygen from the deionised water. A number of papers report [Maryanski et al 1993, Farajollahi 1998, Baldock et al 1998] the use of oxygen-free nitrogen with flow rate of 1000 cc/min for an hour. Our results indicate that it is not necessary to flow for one hour for all experiments. The flow rate and time needed depend on the size of the vessel, flow rate of nitrogen, and total amount of water. If up to 2 litres of gel is prepared, then a flow rate of 800 cc/min, for a total time of 57 minutes is sufficient to reduce the dissolved oxygen to a concentration of 0.1%. If more than 2 litres of gel are to be prepared, then the flow rate and duration need to be increased. A vacuum pump was also used in a trial to eliminate oxygen from the deionised water, and within 5 minutes the oxygen concentration dropped to around 15%, but then it remained constant.

After gel preparation, one of the major problems is to transfer gel from the manufacturing vessel to the phantom or calibration vials. Usually, after preparing the gel, it is kept inside a glove box and then oxygen free nitrogen gases are flowed into the glove box to eliminate oxygen from it. This takes a long time and total manufacturing time becomes lengthy. Another way to transfer gel is using nitrogen pressure [De Deene et al 2000a] and this process has also been used in this study. This process is suitable for transferring small amounts of gel; however, to transfer large volume of gel, a high nitrogen pressure is needed, which opens up the possibility of blowing out the quickfit/rubber bung or to disconnecting the rubber tube. In this study a new method [Figure 4.1] has been used to transfer gel -a pouring method. It is very easy to transfer any amount of gel using this method and there is no any possibility of oxygen contamination. In this study, the oxygen concentration inside the glove box was kept at $\leq 0.2\%$, although a few researchers have maintained $< 0.05\%$ oxygen concentration inside glove box [McJury et al 1999a,b, Hepworth et al 1999]. Several

batches of gel in this study were prepared with >0.05% oxygen concentration inside glove box without, it would seem, detrimental effects. From this study it can be concluded that <0.2% concentration of oxygen inside glove box is sufficient for the manufacture of PAG type gels.

To avoid photo-polymerisation, several groups have used aluminium foil or other lightproof covers to wrap the gel flask [Maryanski et al 1994, Farajollahi 1998]. In this study, gels were prepared inside a dark room to avoid photo-polymerisation due to light (mainly ultraviolet rays). Background R_2 was recorded as 1.16 s^{-1} to 1.50 s^{-1} and sensitivity was recorded as $0.22\text{ s}^{-1}\text{ Gy}^{-1}$ to $0.37\text{ s}^{-1}\text{ Gy}^{-1}$ at room temperature. It has been shown by Maryanski et al [1994] and Farajollahi et al [2000] that the background R_2 and sensitivity were $1.22\text{--}1.28\text{ s}^{-1}$ and $0.85\text{--}1.58\text{ s}^{-1}$, and $0.25\text{--}0.28\text{ s}^{-1}\text{ Gy}^{-1}$ and $0.20\text{--}0.29\text{ s}^{-1}\text{ Gy}^{-1}$ respectively. In reality, background R_2 and sensitivity may vary from batch to batch depending on several factors such as dissolved oxygen inside the gel, temperature at the time of manufacture (the polymerisation reaction is exothermic), photo-polymerisation, chemical composition, purity of the chemicals, length of the stirring time and finally bubbling during preparation. During the early stages of this work the stirring period was 70 minutes, the final bubbling period was 30 minutes and a sensitivity of $0.22\text{ s}^{-1}\text{ Gy}^{-1}$ was achieved. Currently stirring period of 30 minutes and final bubbling period of 40 minutes have to be maintained and the sensitivity achieved is $0.37\text{ s}^{-1}\text{ Gy}^{-1}$. It should be noted that to achieve a highly-sensitive gel, manufacturing time should be short and the last bubbling time should be around 40min (flow rate 150-200 cc/min).

Imaging is one of the crucial parts of the polymer gel dosimeter, and should be fully optimised. It has been shown by many authors [Baustert et al 2000, De Deene et al 2002c] that a multi echo sequence is preferable to a single-echo sequence. However, some authors [Maryanski et al 1994, 1996] prefer the single echo sequence, because they are concerned about errors in measured R_2 values due to application of imperfect refocusing 180° pulses. It has been shown by Baldock et al [2001] that the uncertainty of T_2 determination depends on the echo spacing. They also demonstrated that an echo spacing of 50 ms is more appropriate compared to <50 ms for the range of doses in this study. As a result of this, an echo spacing of 50 ms was used for the multi spin echo sequence and no measurable difference except the scanning time was found between the single echo and multi-echo sequences. Besides the advantage of much shorter scanning time, multi-echo sequences are executed only once and are therefore easier to use and less prone to operator error. On the other hand, single spin

echo sequences have to be executed several times. Different echo times must be set for the scanner before each acquisition, and it is crucial to ensure that the system settings are identical for each echo acquisition. It can therefore be concluded that the MSE sequence is better than single echo sequence for PAG gel dosimetry.

The gel was found to be thoroughly homogeneous after irradiation, as indicated by the measurement of relaxation rates for different tubes at different positions inside scanner. The investigation using 6 tubes of gel has demonstrated that, after irradiation, gel response is uniform and different positions of MRI scanner also show homogenous response. This is in agreement with the results of the investigations carried out by Farajollahi [1998] with un-irradiated gels. This experiment has also demonstrated that the gel temperature increases inside the RF coil during the scan, presumably due to RF power being deposited in the gel.

A calibration curve is essential in order to determine absolute dose distributions. In this study different calibration methods were performed: one was the standard method, where 6/7 identical calibration vials were irradiated to different known doses between 0 to 10 Gy; a second was Oldham's method [Oldham et al 1998b], where two test tubes of gel were irradiated separately in a water bath and the depth dose curve was measured in the gel. The calibration is then determined by fitting the depth-dose measured in water, against the measured change in relaxivity with depth in the gel. The third method used a rectangular shape (20×12×5 cm) Barex™ gel phantom, irradiated in 6 different areas of 4×4 cm to the absorbed doses of 0, 1, 2, 4, 6, and 8 Gy at the centre of the phantom. Our results demonstrate that Oldham's method shows more accurate results with a reduced standard error in comparison with standard method, because the standard methods contain only a few data points, whereas Oldham's method contains many more data points. In addition the standard method requires more gel samples than Oldham's method. One of the major disadvantages of Oldham's method is that the measured R_2 versus depth data has to be compared with central axis depth doses derived from planning data.

The phantom calibration method showed significant differences compared with the standard method. It was thought that this might be due to the temperature difference inside the gel. In order to check this point, the experiment was repeated and the temperature inside the gel was measured during the experiment and another curve for the phantom was drawn after temperature correction. The significant differences remained. The same experiment was done

by Farajollahi et al [2001] who obtained a similar result. Another possible explanation is the temperature difference at the time of irradiation. Since the polymerisation reaction is exothermic, so temperature control is crucial for reproducibility in gel polymerisation. However, Maryanski et al [1994] reported that temperature variation at the time of irradiation has no effect on dose response and this was confirmed by further measurements. Another possible explanation is that the R_2 increase may be due to a contribution from polymer originating from the fresh monomers in the un-irradiated regions migrating to the irradiated region and reacting with long-lived polymer radicals in the irradiated region and this does not occur for the smaller calibration vials.

The dosimeter response in the lower dose region from 0 to 2 Gy, measured in 0.4 Gy intervals, was investigated and found to be linear. At the time of pouring, oxygen concentration inside the glove box was also recorded for different batches of gels and results showed that the variation of oxygen concentration around 0.1 % had no significant effect on sensitivity, and previously mentioned, an oxygen concentration of <0.2% is sufficient to give reproducible results. Gel sensitivity was found to depend on oxygen concentration inside the gel only, not to be influenced by oxygen concentration inside the glove box.

The slope of the dose response curve depends on temperature at the time of scanning, so special attention must be paid to this. It has been reported by Maryanski et al [1995b, 1997a] that a reduction of about $0.01 \text{ s}^{-1}\text{Gy}^{-1}$ in dose response per $^{\circ}\text{C}$ increase occur. In the present study, the sensitivity decrease was found to be $0.011 \text{ s}^{-1}\text{Gy}^{-1}$ per $^{\circ}\text{C}$. Furthermore, a formula was used to compute a temperature corrected dose image. Applying this correction gave a maximum variation of 5% between given and measured dose over a temperature range of 16.2 to 21.1 $^{\circ}\text{C}$.

For any of dosimetric system used in clinical applications it is essential to evaluate the response to beam energy. In section 7.3 it was seen that the dose response of BANGTM gel is independent of energy for a range of commonly used electron and photon energies. This has been reported by several authors [Maryanski et al 1996, De Wagter et al 1996, Baldock et al 1996d, Ibbott et al 1997, Farajollahi et al 1999]. Novotny Jr et al [2001], however, reported an energy dependency of PAG type gel. They irradiated samples up to 6.37 Gy and reported that gel sensitivity depended on absorbed energy. The present study of dose response of PAG dosimeter as a function of beam energy demonstrated that the gel dose response is

independent of energy in the range of 4 to 15 MeV electron compared with 6 MV x-rays. In our results up to 6 Gy [figure 4.23] show no energy dependence at least for electron energies from 4-15 MeV and 6 MV x-rays. From figure 4.23, it can be said that the response of PAG gel shows no significant difference [$P>0.05$, ANOVA]. Measured electron energies using PAG show good agreement with ionisation chamber measurements. For ionisation chamber measurements it is difficult to place a chamber at an exact depth. Uncertainty in the depth can be 1 to 2 mm, and for the difference of 1 mm depth, the energy difference is 0.2 MeV. Recently Biggs [2003] reported measurements made over a five years period showing that energy differences of 2.1 to 3.5 % were seen for 6, 9, and 12 MeV electrons. Given these energy variations, we have no evidence that the PAG is energy dependent, at least up to 12 MeV electron energy.

During radiotherapy, the presence of bone will cause a greater reduction in dose to the soft tissue beyond the bone, compared to the situation when no bone is present. In the present study bone equivalent gels with a density of 1.2 gm/cc were prepared using a calcium salt; the response was found to be linear up to at least 10 Gy. However, bone density is in the range of 1.2-1.8 gm /cm³ depending on whether it is spongy or compact, so the gels must be developed further in order to achieve a higher density whilst remaining solid at room temperature.

Chapter 5

Normoxic Polymer Gels

5.1 Introduction

In the last few years, polymer gels have been used to measure complex dose distributions in three dimensions, for example in brachytherapy applications [Maryanski et al 1996, McJury et al 1999b, Farajollahi et al 1999, Papagiannis et al 2001], stereotactic radiosurgery [Ibbott et al 1997, Meeks et al 1999, Ertl et al 2000, Pappas et al 2001], intensity-modulated radiotherapy [Oldham et al 1998a, De Deene et al 2000d], cardiovascular brachytherapy [Amin et al 2001, Baras et al 2002]. However, it is still not widely used in clinical situations or for routine quality assurance. One of the reasons for this is that polymer gels are difficult to manufacture. For research purposes, two types of gel have been used: Fricke gel and BANG[®] or PAG gel. Both have their limitations as has been discussed previously.

Recently, a new polymer gel dosimeter has been reported in the literature [Fong et al 2001]. This gel, which has the acronym MAGIC (**M**ethacrylic and **A**scorbic acid in **G**elatin **I**nited by **C**opper) can be manufactured more easily than previous formulations. In their study, Fong and co-workers used Gelatin (300 bloom) as a gelling agent, Methacrylic acid (MAA) as monomer, and HPLC grade water as solvent. They also used copper-sulphate ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$) and ascorbic acid which form a complex with oxygen, and serves as a free radical source for the initiation of the polymerisation of methacrylic acid. Hydroquinone was used to keep the monomer from auto-polymerisation and to absorb any free radicals introduced from the gelatin or other components, which could initiate polymerisation before irradiation. They used different concentrations of monomer and their result shows that the dose response curve was linear up to 30 Gy and the slope of R_2 versus dose at 20 MHz was 0.3, 0.519 and $0.681 \text{ s}^{-1} \text{ Gy}^{-1}$ respectively for MAA concentration of 3, 6, and 9%. It has also been reported by Fong et al [2001] that the slope of the calibration curve increased with increasing magnetic field strength. A similar sort of study was performed by Gustavsson et al [2001], with the difference that they did not use hydroquinone, but showed very similar results. In another study, Gustavsson et al [2003] also used MAGIC type gel to investigate intensity modulated radiation therapy treatment verification. They also reported that their measured data was in good agreement with the radiotherapy treatment plan. ✓

In another study, the stability of polymer gel dosimeters, including MAGIC gel, was investigated by De Deene et al [2002a]. Their results show that the stability of the R_2 dose response is largely determined by the chemical composition of the gel dosimeters. They also showed that the compactness of the gelatin matrix has an effect on both the dose sensitivity and the R_2 value of an unirradiated gel sample (background R_2) and on the rate of post-irradiation polymerisation. In addition, De Deene et al [2002a] reported that whilst the R_2 -dose sensitivity for PAG gels increases with time (post irradiation), it decreases with time for MAGIC gel, which indicates that the polymer structure in the normoxic gels differs from the polymer structure in the PAG gels. In their study, De Deene and co-workers recommended a waiting period of 10 hrs between irradiation and scanning for the PAG gel and 30 hrs for the MAGIC gel. At the same time, a chemical analysis of MAGIC gel was also performed by De Deene et al [2002b], where the radiation response for gels with different compositions was evaluated. Their results show that some initial polymerisation takes place due to the creation of radicals from the ascorbate-copper-oxygen complex. They also showed that without Cu^{2+} , ascorbic acid is able to scavenge oxygen but at a much slower rate. Hydroquinone used in low quantities may facilitate the radiation-induced polymerisation reactions, but at high concentrations it will operate as an inhibitor. They also investigated another five anti-oxidants and only three of them were found to scavenge the oxygen.

This chapter reports the results of initial investigations of the properties of the MAGIC gel, including the linearity of the dose response, stability with time, dependency of the gel on electron energy, polymer diffusion, temperature dependency of R_2 and the effects of phantom wall materials.

5.2 Methods

5.2.1 Gel preparation

The “MAGIC” gel was manufactured using the formulation proposed in the literature [Fong et al 2001] with no additional precautions to exclude oxygen.

For the preparation of MAGIC gel, type A gelatin from porcine skin approximately 300 bloom [Sigma Ltd] was used. Some batches of gel were also prepared using the same type of gelatin supplied by Aldrich Ltd. As a monomer, methacrylic acid [Sigma Ltd] was used. Methacrylic acid from Aldrich was also used for a few batches of gel. As an anti-oxidant, L-ascorbic acid [Aldrich Ltd] was used in this study. Copper sulphate pentahydrate ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$) [Aldrich Ltd], Hydroquinone [Sigma Ltd] and HPLC (High pressure liquid

chromatography) water [Aldrich Ltd, purity level, evaporation residue <0.0003%] were also used to prepare the gels. The procedures were carried out in normal atmospheric conditions. For the preparation of 100 gm gel, the components are listed in table 5.1.

Component	Amount (g)
HPLC water	82.8
Gelatin (300 bloom)	8
Methacrylic acid	9
Hydroquinone	0.198
L-Ascorbic acid	0.0352
CuSO ₄ ·5H ₂ O	0.002

Table 5.1 Composition of 100 g MAGIC gel.

The preparation of MAGIC gel is simpler than for PAG gels. For the former, there is no need to use an oxygen free glove box or nitrogen for purging oxygen from the gel. In order to make 100 ml of MAGIC gel, 70 ml of HPLC water was placed in a conical flask. 8 gm of gelatin (8% by weight) was added to the water, and the flask was subsequently placed in a water bath at 50 °C to ensure that the gelatin was completely dissolved. A magnetic stirrer bar was then placed inside the flask, 0.198 gm hydroquinone in 4.8 ml of water was added, and the solution was stirred until the hydroquinone was dissolved. The flask was then placed in a water bath at 37 °C to allow the solution to cool. When the solution had cooled to approximately 37 °C, L-ascorbic acid (0.0352 gm in 5 ml of water) and CuSO₄·5H₂O (0.002 gm in 3 ml of water) were added and the solutions were stirred for a few minutes, before 9 gm of methacrylic acid (9%) was added. Then the solution was stirred until the mixture was fully dissolved. Finally, the gel was transferred to phantoms and/or calibration vials as required and all the vessels were placed in an ice water bath or refrigerator for solidification. The total preparation time was approximately one hour.

5.2.2 Imaging

MR images were measured using a 1 T whole-body scanner using the standard quadrature knee coil for signal reception. The transverse relaxation rate R_2 ($1/T_2$) of the water protons was taken as a measure for the calculation of absorbed dose in the gel. Gel samples were placed in the MR room 24 hours prior to measurement, to obtain temperature equilibrium. Imaging was usually undertaken 1 to 5 days after irradiation. Both spin-echo and multi spin-

echo sequences were used in this study. For the spin echo sequence, a repetition time of 3000 ms was used with echo times of 25, 50, 75, and 100 ms. The field of view (FOV) was 192 mm for 0.75 mm in-plane resolution and 300 mm for 1.17 mm in-plane resolution and the matrix size was 192×256. Slice thickness was 3 to 10 mm depending on the type of measurement, and transverse, sagittal, and coronal images were generated. Acquisition time was 580 s for each echo time.

For the multi spin echo sequence, an echo train length of 16 was used with an initial echo time of 22.5 ms, and fifteen 22.5 ms increments. Repetition time was 3000 ms, field of view was 300 mm with a matrix size of 192×256. slice thickness was again 3-10 mm and in-plane resolution was 1.17 mm. For generating R_2 images, the first two (22.5, 45 ms) and the last few echo times (due to the very low signal at higher dose level) were discarded to minimise any image imperfections. The images were transferred from the MRI computer to a Sun Microsystems workstation (Palo Alto, CA, USA) for generating R_2 and dose images and for further analysis. Details of this were described in section 4.6.

5.3 Basic properties of the MAGIC gel

This section describes the practical aspects of the MAGIC gel dosimetry including the choice of pulse sequence, linearity of the dose response and stability with time, dependency on electron energy, polymer diffusion, temperature dependency of R_2 for MAGIC gel and the effects of the phantom wall materials.

5.3.1 Long term effect on background R_2

In order to investigate the effect of time from manufacture to MRI measurement on background R_2 , two glass tubes (length 100 mm and outer diameter 25 mm) were filled with gel from the same batch. The resulting transverse relaxation rates (R_2) of the un-irradiated gels were measured 6 h after manufacture. Several measurements were then made up to 56 days after manufacture.

Figure 5.1 shows the variation of background R_2 with time after manufacture, with R_2 increasing up to 32 days after manufacture.

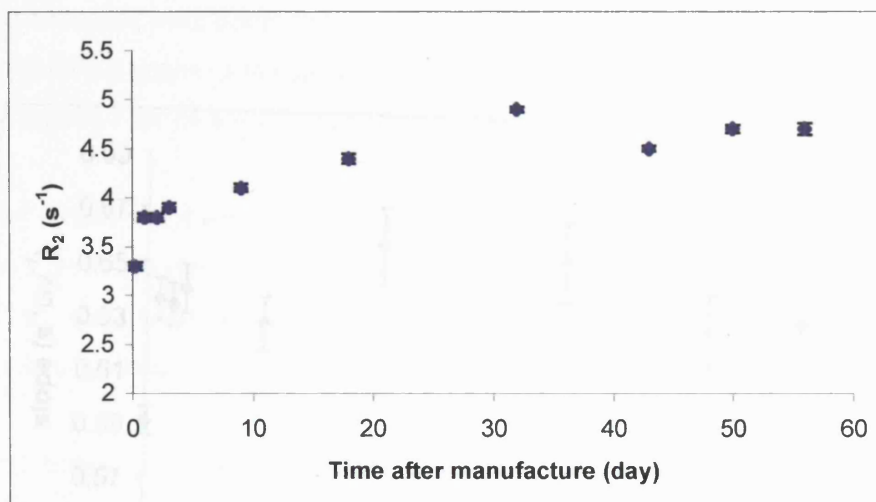


Figure 5.1 R_2 values obtained in the un-irradiated gel at different times after manufacture.

Error bars represent the standard deviation within the circular region of interest used to measure R_2 .

5.3.2 Long-term effect on dose response of the gel

In this section the dependence of the dose response on time from irradiation to measurement was investigated. To do this, 500 ml gel was prepared and then 8 calibration vials were filled with gel. Vials were irradiated using 6 MV x-rays from 0-50 Gy 3 hrs after manufacture. The resulting transverse relaxation rates (R_2) of the polymerised gels were measured 2 h after irradiation. Several measurements were then made up to 56 days after the initial irradiation.

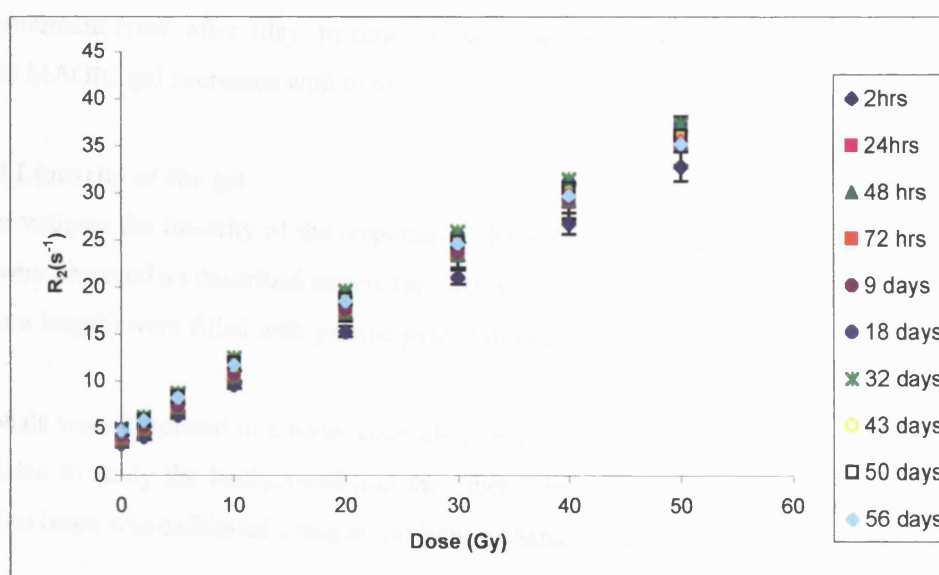


Figure 5.2 Dose response curve of MAGIC gel up to 8 weeks post-irradiation

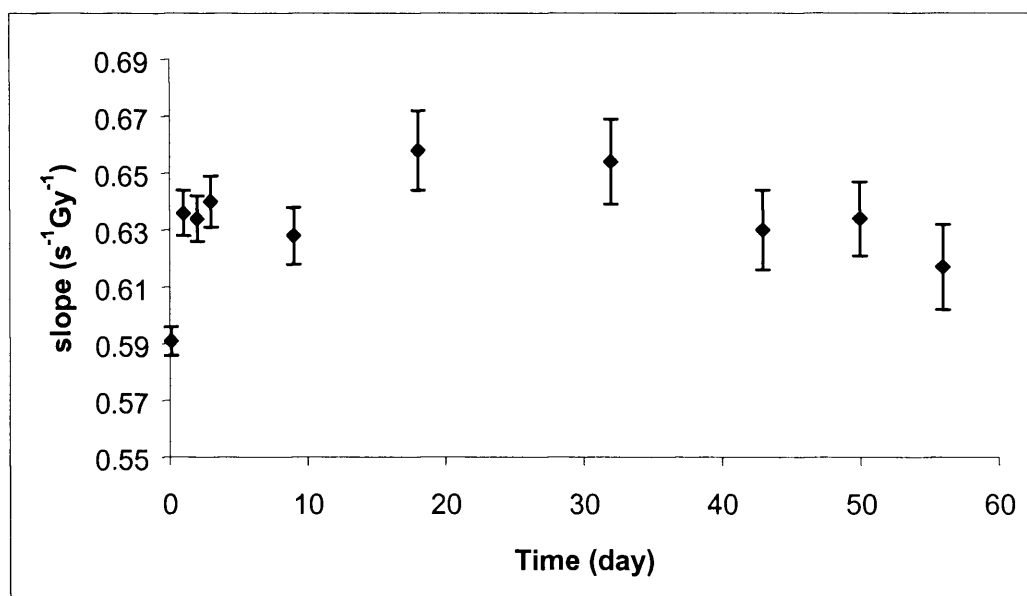


Figure 5.3 Slope of the linear portion of the R_2 versus dose plot at different times after irradiation.

Figure 5.2 illustrates the R_2 versus dose curve for different times post irradiation. After the initial measurement at 2 hrs, the R_2 values were almost constant from 1 to 56 days. The slope of the R_2 -dose curve of gel at different times after irradiation is displayed in Figure 5.3. From the result it can be seen that the response of the MAGIC gel remains constant within measurement error, after 1 day. In contrast De Deene et al [2002a] reported that the response of the MAGIC gel decreases with time.

5.3.3 Linearity of the gel

To investigate the linearity of the response of the MAGIC gel with absorbed dose, 500 ml of gel were prepared as described earlier (section 5.2.1). Eight glass vials (25 mm diameter and 100mm length) were filled with gel and placed in an ice-water bath to solidify.

The vials were irradiated in a water equivalent phantom using 6 MV x-rays. One was left un-irradiated to study the background and the other 7 irradiated with absorbed doses up to 50 Gy. The beam was calibrated using an ionisation chamber, as described in chapter 4 (4.8.1).

R_2 measurements were performed one day after irradiation, using a knee coil and the vials were placed in a polystyrene box inside the coil. After irradiation, the vials were kept outside the refrigerator for 24 hours to equilibrate to room temperature.

Another 6 vials of gel were prepared from a different batch of gels to study the linearity in the lower dose region (0-3Gy). Gels were irradiated using 6MV x-rays with the dose of 0, 1, 1.5, 2, 2.5, and 3 Gy 4 days after manufacture and scanned 7 days after irradiation using the multi spin echo sequence.

Figure 5.4 shows the dose response curve of MAGIC gel, which is linear up to 50 Gy. The linear fit parameters of the dose response curve were $R_2 = (0.64 \pm 0.01) D + (3.96 \pm 0.21)$ ($R^2 = 0.999$), where D is the absorbed dose. Figure 5.5 shows the dose response curve in the lower dose region (0-3Gy). It is linear and the slope of this dose response curve was $0.38 \pm 0.01 \text{ s}^{-1} \text{ Gy}^{-1}$ with $R^2 = 0.99$. The large difference (approximately 50%) between the two measurements may be due to the batch difference, and the use of different pulse sequences. ✓

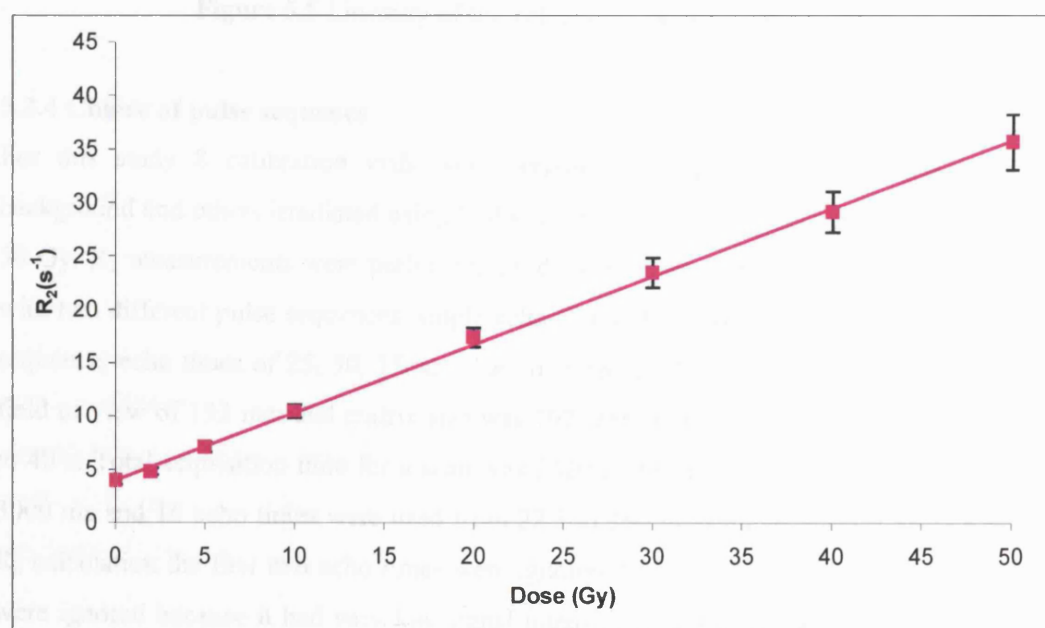


Figure 5.4 Dose response curve for MAGIC gel.

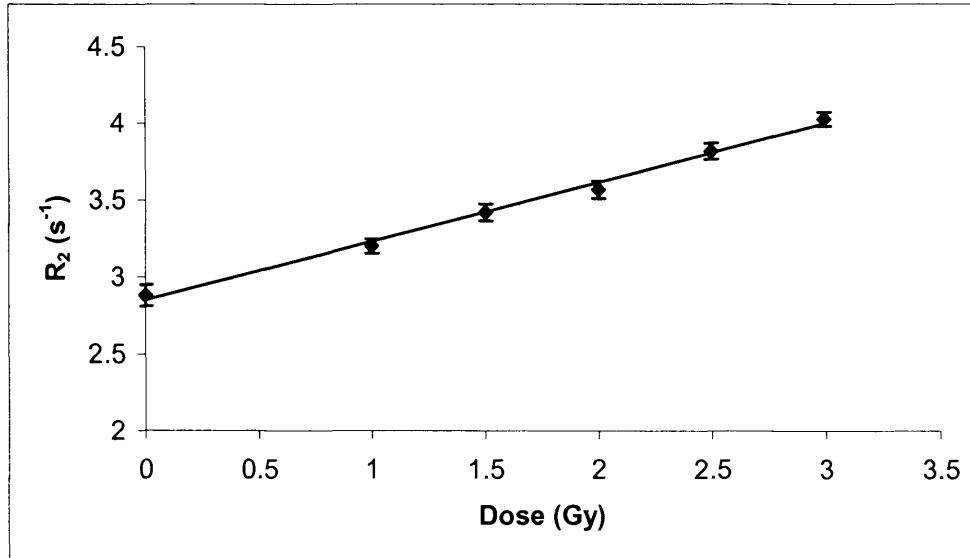


Figure 5.5 Linearity of the gel dose response from 0 to 3 Gy

5.3.4 Choice of pulse sequence

For this study 8 calibration vials were prepared with gel, one left un-irradiated as a background and others irradiated using 6 MV x-rays to absorbed doses of 2, 5, 10, 20, 30, 40, 50 Gy. R_2 measurements were performed 56 days after irradiation using a 1T MRI scanner with two different pulse sequences: single echo and multi-echo sequence. For the single echo sequence, echo times of 25, 50, 75, and 100 ms were used. The TR value was 3000 ms with field of view of 192 mm and matrix size was 192×256. For each echo time, scan time was 9 m 40 s. Total acquisition time for a scan was 2320 s. For the multi-echo sequence, TR was 3000 ms and 16 echo times were used from 22.5 to 360 ms with an interval of 22.5 ms. For R_2 calculation the first two echo times were ignored due to pulse imperfections and last few were ignored because it had very low signal intensity. Images were acquired with a field of view of 192 mm, matrix size of 256×256 and in-plane resolution was 0.75×0.75 mm; the total scan time was 769 s.

Figure 5.6 shows the dose response curve for both spin echo and multi-spin echo sequence. Linear fits for spin echo sequence and multi-echo sequence were $R_2 = (0.62 \pm 0.01)D + (5.20 \pm 0.38)$ ($r^2=0.997$) and $R_2 = (0.48 \pm 0.02)D + (2.81 \pm 0.43)$ ($r^2=0.993$) respectively. This

result shows that dose sensitivity for the single spin echo sequence is higher than that for the multi-echo sequence. Since, after applying a third R.F. pulse a stimulated echo is observed [Hahn 1950] which only affects multi-spin echo sequences and propagates through the echo train, this can result in an inaccurate measured R_2 . However, for single echo sequence, no stimulated echo is generated, thus gives accurate R_2 values if different is not an issue.

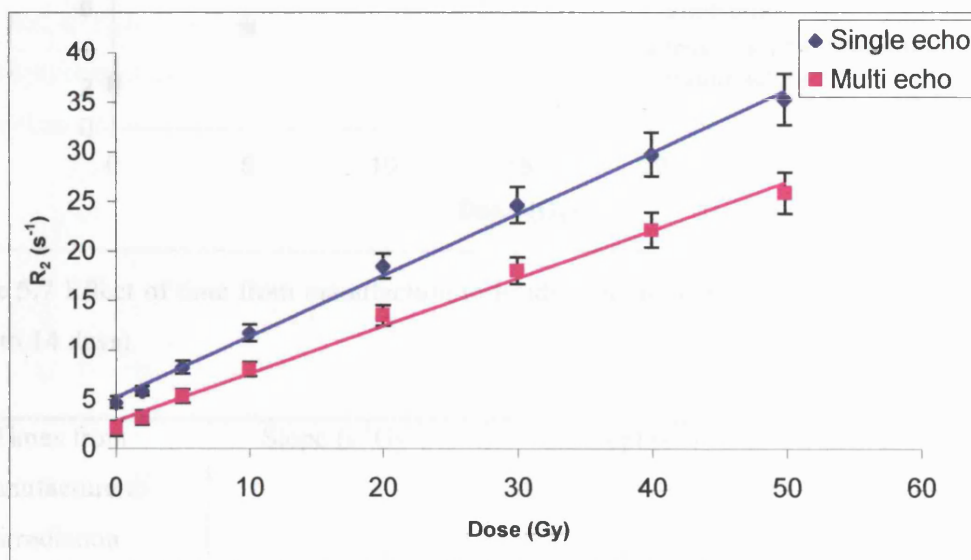


Figure 5.6 Dose response curve for spin echo and multi spin echo sequence.

5.3.5 Effect of time from manufacture to irradiation

In this study, the effect of time from manufacture to irradiation was investigated. Eighteen calibration vials were prepared with gel from same batch. Three vials from each batch were left unexposed as a background and five vials were irradiated 1 day and the other five vials were irradiated 6 days and final five vials were irradiated 14 days after manufacture. The irradiations were made using 6 MV x-rays with a field size of 15 x 15 cm and SSD of 95 cm and in all cases, the absorbed dose ranged from 5 to 25 Gy. In all cases, scanning was performed 1 day after irradiation.

The dose response curves for gels irradiated 1 day, 6 days and 14 days after manufacture are shown in figure 5.7. Table 5.2 shows the slope of the dose response curve for irradiation 1 day, 6 days and 14 days after manufacture. The dose response remains almost constant, with small variation of intercepts (background) with time. It can be seen that there is significant effect on time from manufacture to irradiation at least up to 14 days.

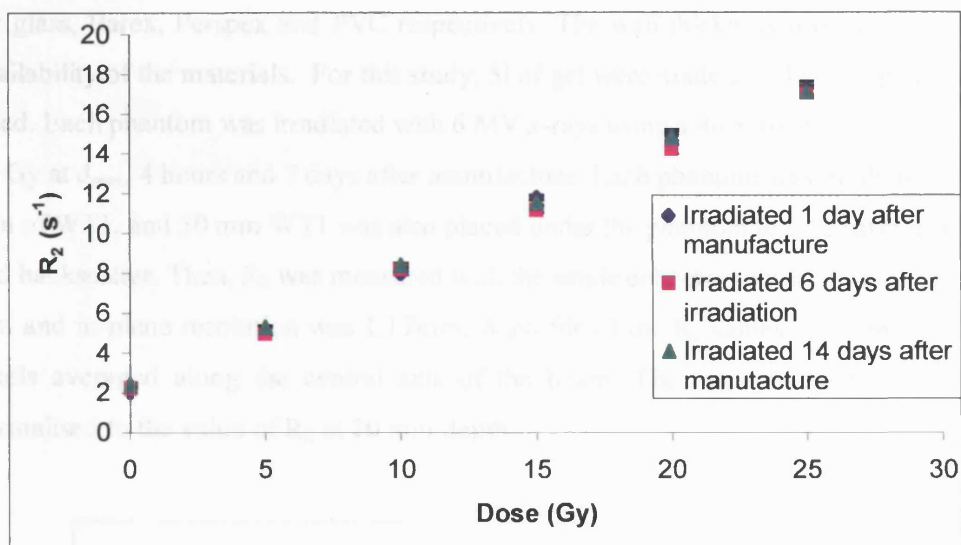


Figure 5.7 Effect of time from manufacture to irradiation on the dose response of MAGIC gel (1 to 14 days).

Times from manufacture to irradiation	Slope (s ⁻¹ Gy ⁻¹)	Intercept (s ⁻¹)	r ²
1 day	0.63 ± 0.02	2.00 ± 0.27	0.99
6 days	0.60 ± 0.01	2.13 ± 0.10	0.99
14 days	0.60 ± 0.01	2.43 ± 0.20	0.99

Table 5.2 Variation of dose response with time from manufacture to irradiation.

5.3.6 Investigation of the effect of phantom wall material on MAGIC gels

The use of plastic phantoms for PAG gel often gives rise to inhibited radiation-induced polymerisation at the surface, but this effect is not observed when glass and Barex are used [Maryanski et al 1994, Bonnett et al 1999, Haraldsson et al 2000]. The same problem for normoxic gels would not be expected, but it is important to investigate the effect of phantom material for use with normoxic MAGIC gels. In this experiment, the effects of different phantom wall materials such as Barex, PVC and Perspex were investigated and compared with glass phantom wall.

For this study glass, Barex, PVC and Perspex phantoms were prepared each with outer dimensions of 200 x 120 x 50 mm. The wall thickness was 2.4 mm, 1 mm, 3 mm and 2 mm

for glass, Barex, Perspex and PVC respectively. The wall thickness was determined by the availability of the materials. For this study, 5l of gel were made and the four phantoms were filled. Each phantom was irradiated with 6 MV x-rays using a 40 x 40 mm field and a dose of 20 Gy at $d_{\max}$, 4 hours and 7 days after manufacture. Each phantom was irradiated behind 25 mm of WT1, and 50 mm WT1 was also placed under the phantom to give sufficient build-up and backscatter. Then, R_2 was measured with the single echo sequence. Slice thickness was 5 mm and in-plane resolution was 1.17mm. A profile of the R_2 values were obtained using 3 pixels averaged along the central axis of the beam. The response of the gel was then normalised to the value of R_2 at 10 mm depth.

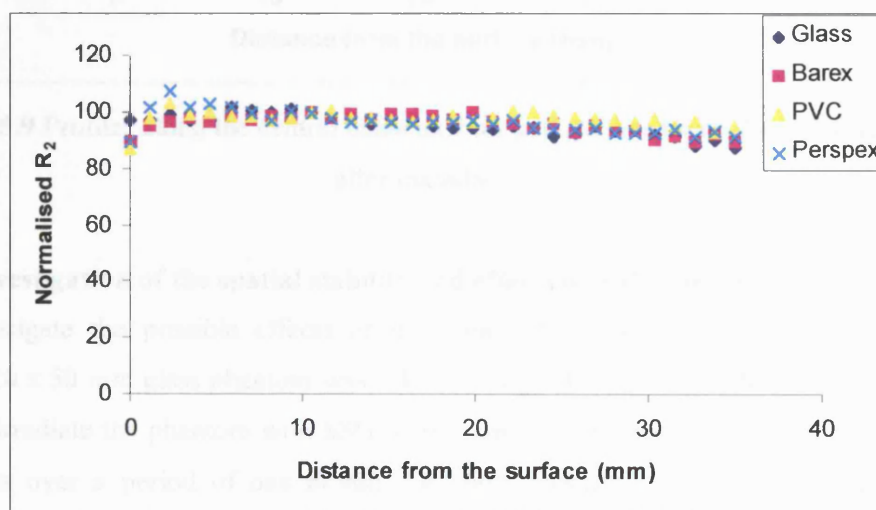


Figure 5.8 Profiles along the central beam axis for gel irradiated with 20 Gy x-rays, 4 hours after manufacture.

The central axis depth dose curves for the 4 phantoms are shown in Figures 5.8 and 5.9. Here, all data are normalised at 10 mm from the surface of the phantom, and show that the wall material of the phantom did not effect polymerisation, even gels irradiated 4 hours (figure 5.8) and 7 days (figure 5.9) after manufacture show almost the same results. In both cases noise was observed at the edge of all phantom, possibly due air bubbles at the edges. It should be noted that a few polymerised areas were observed at the top of the phantom, indicating that still oxygen plays a significant role.

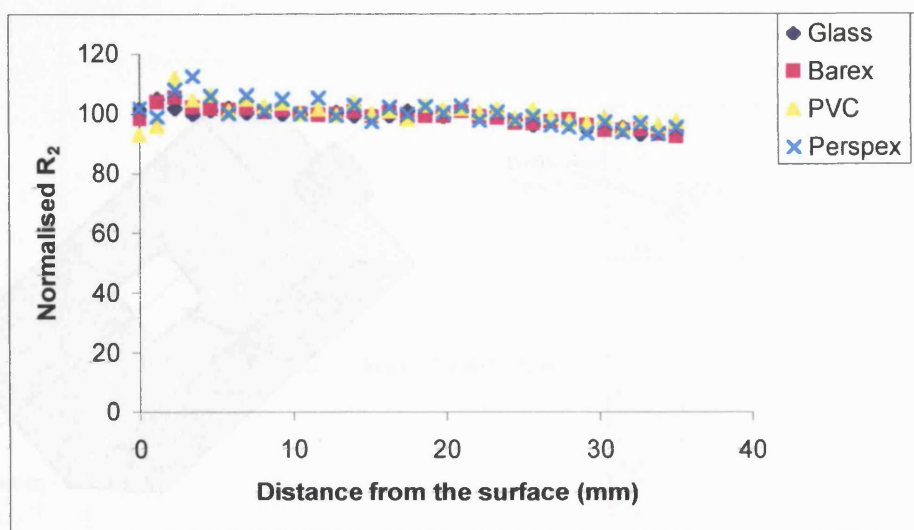


Figure 5.9 Profiles along the central beam axis for gel irradiated with 20 Gy x-rays, 7 days after manufacture.

5.3.7 Investigation of the spatial stability and effects of diffusion on resolution

To investigate the possible effects of diffusion, 1400 ml of gel was prepared and a 200 x 120 x 50 mm glass phantom was filled. A single 40 x 40 mm 6 MV photon field was used to irradiate the phantom with SSD of 100 cm. R_2 imaging was performed on several occasions over a period of one month. On each occasion, a single coronal image was performed, with the slice positioned at the centre of the irradiated area [Figure 5.10]; the slice thickness was 5 mm and in-plane resolution was 1.17 mm. Profiles were measured at the centre of the coronal image [Figure 5.10] and 5 pixel values were averaged from where the width of the polymerised area was measured. Temperature was recorded at the time of scanning, and was between 18.9 °C and 20.7 °C.

Figure 5.11 shows the dose profile measured on several occasions up to 56 days after irradiation, while Table 5.3 lists the estimated width of the irradiated region. The estimated width of the irradiated region (FWHM) decreased by 14% over 56 days. This result was verified by repeating the experiment twice. In these two subsequent experiments, the width of the irradiated region decreased by 14% over 34 days and 12% over 25 days. It can be seen from figure 5.11 that increased dose was observed at the edge of the irradiated area after one day. The dose overestimation was 11% at 4 days and the maximum overestimation was 16%. The dose overestimation was also observed by Maryanski et al [1994] and De Deene et al [2001] for PAG gel.

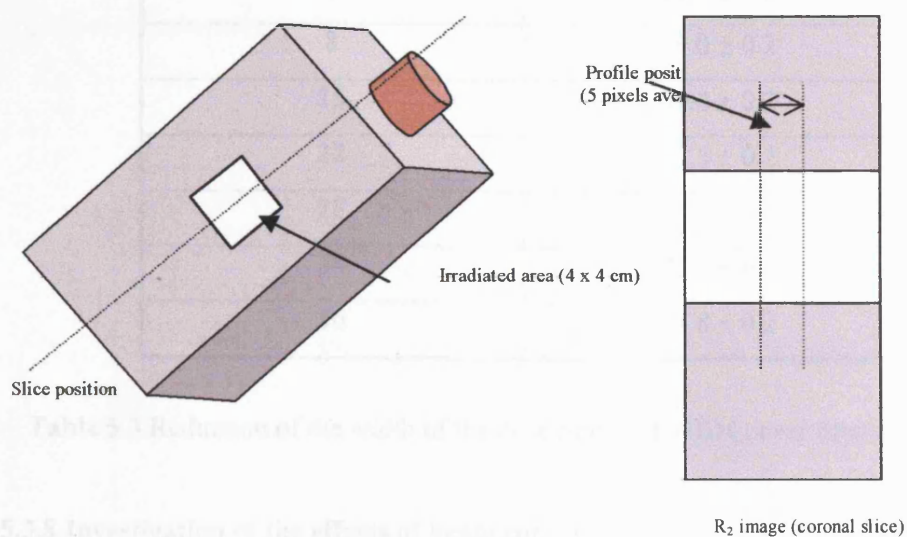


Figure 5.10 Diagram of irradiated phantom (200 x 120 x 50 mm) with slice position and R_2 image with profile position.

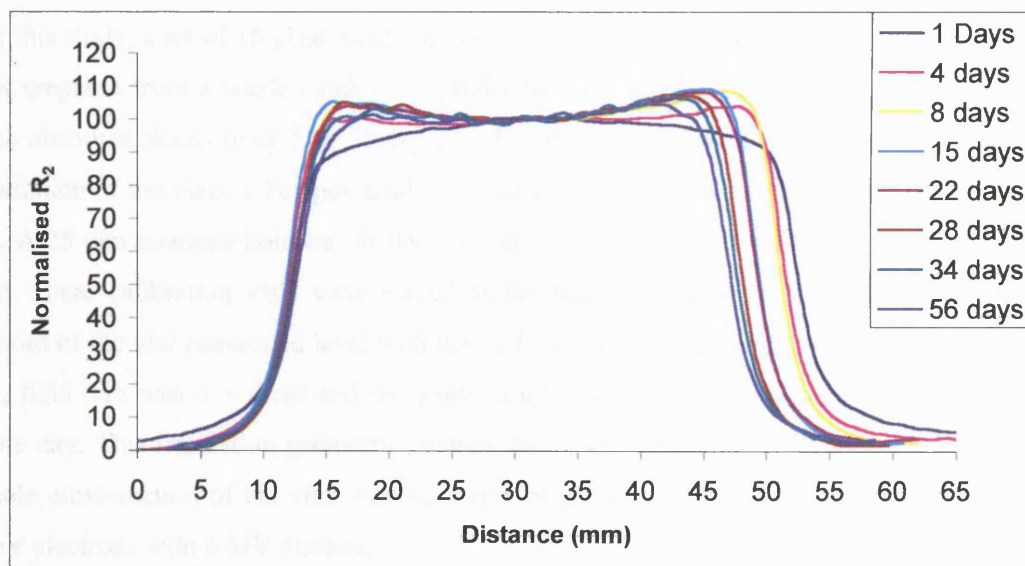


Figure 5.11 Profile of R_2 across the central irradiated area measured on several occasions over a period of one month after irradiation.

Time after irradiation (day)	Measured width (mm)
1	40.3 ± 0.2
4	39.7 ± 0.2
8	39.0 ± 0.2
15	37.8 ± 0.2
22	37.5 ± 0.2
28	36.0 ± 0.2
34	35.5 ± 0.2
56	34.8 ± 0.2

Table 5.3 Reduction of the width of the dose profile (FWHM) over time after irradiation.

5.3.8 Investigation of the effects of beam energy

For any dosimetric system used in clinical applications it is essential to evaluate the response of the system to different beam energies. This study is focused on evaluation of the dependence of MAGIC type polymer gel dosimeter response to different electron beam energies from a linear accelerator.

For this study, a set of 16 glass vials 100 mm long, 25mm outer diameter and 1mm thick wall was prepared from a single batch of gel and irradiated using 6, 8, 10 and 12 MeV electrons with absorbed doses from 5 to 30 Gy one day after manufacture. To ensure homogeneous irradiation of the vials, a Perspex holder was constructed with the dimension of $20 \times 20 \times 10$ cm. A 25 mm diameter hole was drilled through the central axis of the holder to a depth of 15 mm where calibration vials were placed at the time of irradiation [Figure 5.12] with the bottom of the vial positioned level with the surface. Irradiations were made with a SSD of 95 cm, field size was 6×6 cm and the gantry angle was 90° . All vials were irradiated on the same day. This irradiation geometry ensured that at any depth, the dose was uniform on the whole cross-section of the vial. Another batch of gel was prepared for use in comparing 12 MeV electrons with 6 MV photons.

Evaluation of the gel was performed 3 days after irradiation. All vials were left out from the refrigerator for 24 hours before their evaluation to equilibrate to room temperature. For all vials, sagittal images were produced at the central axis of the calibration tubes. R_2 images were prepared as described previously in section 4.6. To obtain the R_2 values for different

dose levels at different electron energies, depth dose curves were produced for each energy. Depth dose curves were produced along the central axis of the gel vials and averaged over three pixels. R_2 values were measured at the maximum dose level of each depth dose curve of each electron energy.

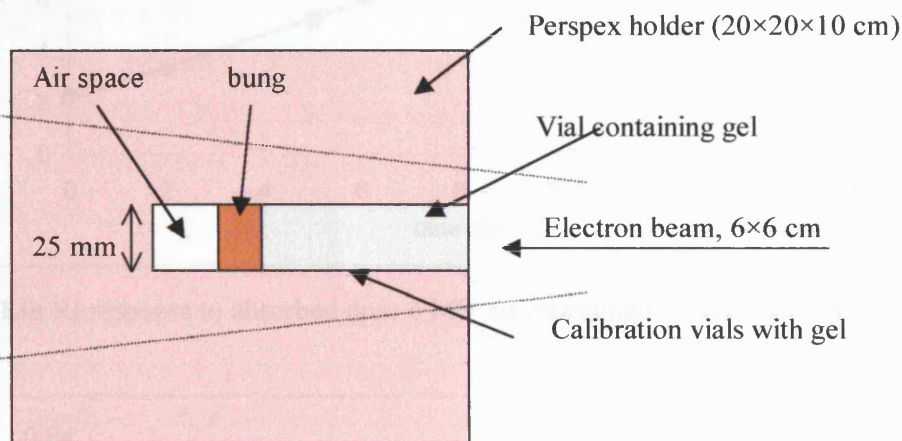


Figure 5.12 Cross-sectional view of Perspex holder used when irradiating calibration tubes for different electron energies and electron doses.

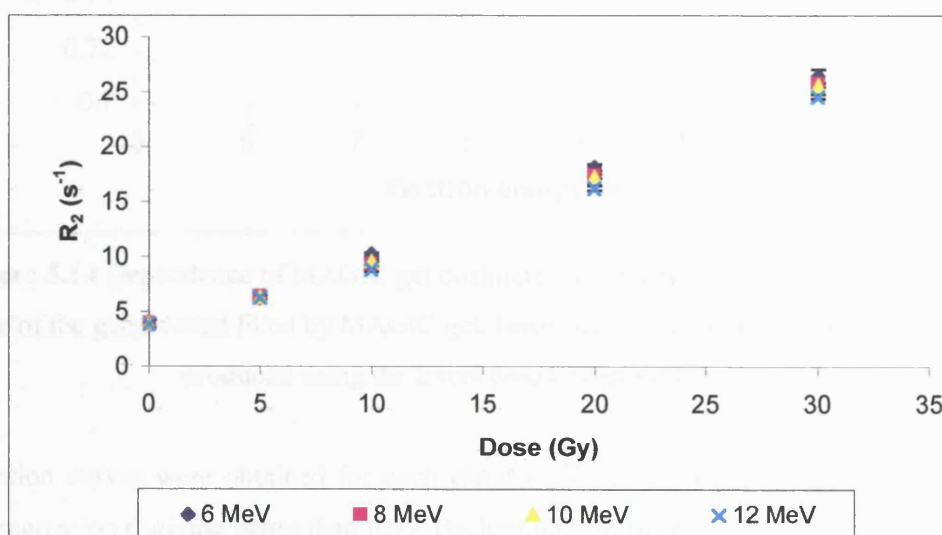


Figure 5.13a R_2 response to absorbed dose for electrons in the energy range of 6-12 MeV at 2 MeV intervals. The error bars were estimated from different depth dose profiles through the image data at different off axis positions.

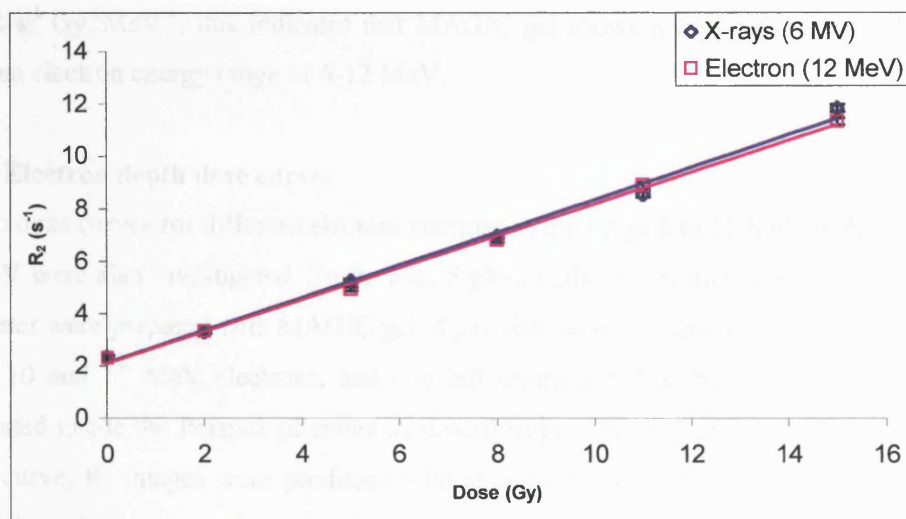


Figure 5.13b R_2 response to absorbed dose 6 MV x-rays compared with 12 MeV electrons.

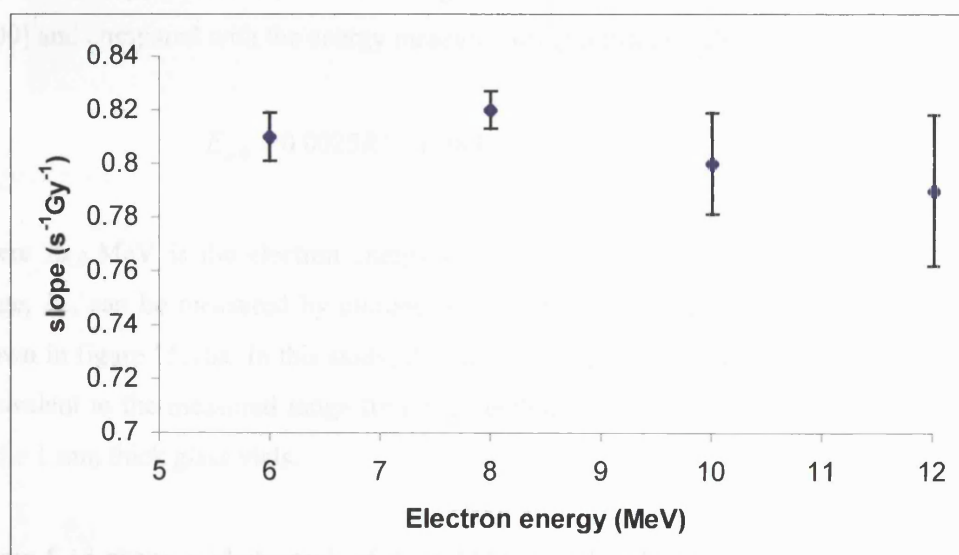


Figure 5.14 Dependence of MAGIC gel dosimeter sensitivity on electron energy in the centre of the glass vessel filled by MAGIC gel. Error bars represent the standard deviation produced using the Excel based program Linest.

Calibration curves were obtained for each electron energy as shown in figure 5.13a with linear regression r^2 giving better than 0.99. Backgrounds in figure 5.13a were excluded from the calculation of the slope due to their lower accuracy. Figure 5.13b shows R_2 response to absorbed dose for 6 MV x-rays compared with 12 MeV electrons. Results show different dose response and different background. The difference between the two measurements may be due to the batch difference, and the use of different pulse sequences. Figure 5.14 shows the slope of the dose response curve versus electron energy; the slope of this plot is $-0.004 \pm$

$0.002 \text{ s}^{-1} \text{ Gy}^{-1} \text{ MeV}^{-1}$; this indicates that MAGIC gel shows a negligible energy dependency over an electron energy range of 6-12 MeV.

5.3.9 Electron depth dose curves

Depth dose curves for different electron energies in the range 6 to 12 MeV with an interval of 2 MeV were also investigated. To do this, 5 glass vials of 100 mm length and 25 mm outer diameter were prepared with MAGIC gel. 4 gel vials were irradiated using 20 Gy at $d_{\max}$ with 6, 8, 10 and 12 MeV electrons, and one left un-irradiated as background. Gel vials were irradiated inside the Perspex phantom as described previously (see 5.3.8). To draw the depth dose curve, R_2 images were produced with slice thickness of 5 mm and 0.75 mm in-plane resolution. Depth dose data were measured along the central axis of the gel vials and averaged over 5 pixels and finally background R_2 was subtracted from the measured data. Electron energies were calculated using the following equation [Williams and Thwaites 2000] and compared with the energy measured using ionisation chamber:

$$E_{p,0} = 0.0025R_p^2 + 1.98R_p + 0.22 \quad (5.1)$$

where $E_{p,0}$ MeV is the electron energy and R_p is the practical range in cm. The practical range, R_p , can be measured by plotting measured dose on y-axis versus depth on x-axis as shown in figure 5.16a. In this study, the electron range used to measure electron energy was equivalent to the measured range from the depth dose curve plus the water equivalent depth of the 1 mm thick glass vials. ✓

Figure 5.15 shows a photograph of the 5 MAGIC gel vials; one left un-irradiated (left side) and other 4 irradiated using 20 Gy electrons with energies of 6, 8, 10, and 12 MeV. The depth dose curves are shown in figure 5.16a. Figure 5.16b shows a depth dose curve for 12 MeV electron produced from MAGIC gel and compared with radio chromic data. Table 5.4 shows the measured electron energy using MAGIC gel, ionisation chamber and radiochromic film. It can be seen that there was reasonable agreement between the gel and the ionisation chamber. The radiochromic film gave the highest value for the electron energy.



Figure 5.15 Photograph of 5 MAGIC gel vials, one left un-irradiated (left side) and the other 4 irradiated using 20 Gy of electrons with energies of 6, 8, 10 and 12 MeV.

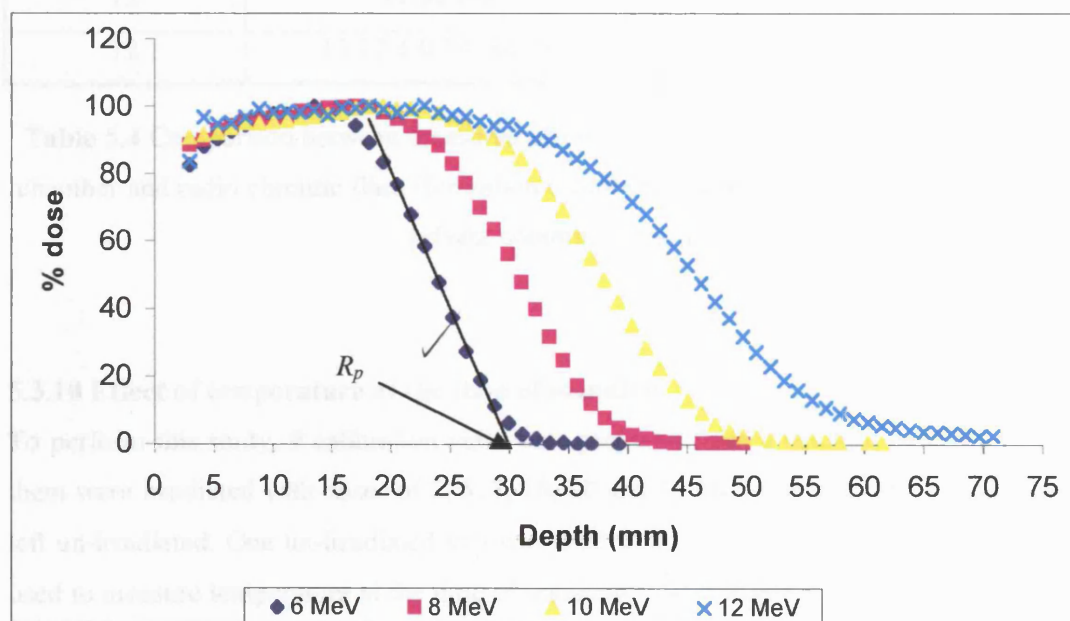


Figure 5.16a Depth dose curves for different electron energies

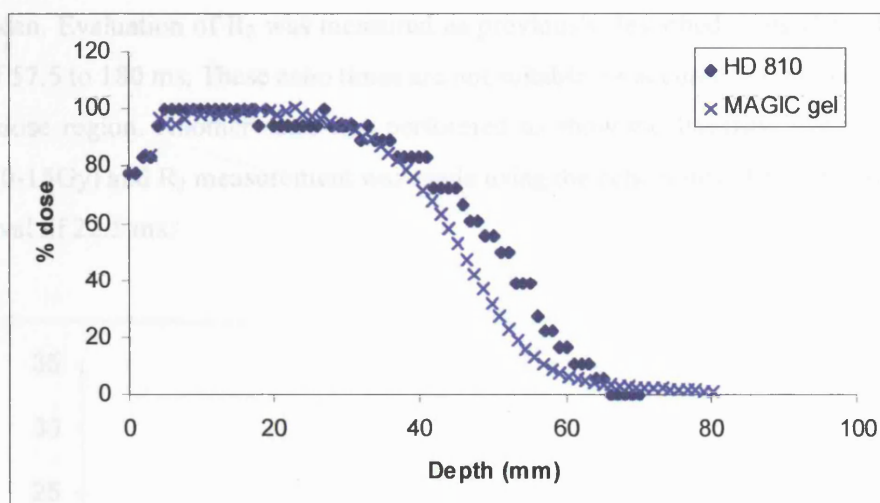


Figure 5.16b Depth dose curve for 12 MeV electron produced using MAGIC gel and GAF chromic HD 810 film.

Nominal Energy (MeV)	Measured energy (MeV) using MAGIC gel	Measured energy (MeV) using ionisation chamber
6	6.28 ± 0.20	6.38 ± 0.20
8	7.91 ± 0.20	8.58 ± 0.20
10	9.68 ± 0.25	10.58 ± 0.25
12	11.92 ± 0.25	12.65 ± 0.25
12	13.12 ± 0.30 (HD 810)	

Table 5.4 Comparison between measured electron energies using MAGIC gel, ionisation chamber and radio chromic film. (Ionisation chamber measurements courtesy of S Bolton: private communication)

5.3.10 Effect of temperature at the time of scanning

To perform this study, 9 calibration vials were prepared from a batch of MAGIC gel. 6 of them were irradiated with doses of 2, 5, 7, 10, 20 and 30 Gy 1 day after manufacture and 3 left un-irradiated. One un-irradiated vial was used as a background and the other two were used to measure temperature at the time of scanning. The evaluation of the calibration tubes was performed 7 days after irradiation. In order to reduce the scanning time and ensure that temperature was relatively constant during a scan, a multi echo sequence with 16 equally spaced echoes was used to create R_2 images. The temperature inside the vials was measured before and after each MR image acquisition and averaged to estimate temperature at the time

of the scan. Evaluation of R_2 was measured as previously described using data at the echo times of 57.5 to 180 ms. These echo times are not suitable for accurate R_2 measurement of 0-10 Gy dose region. Another scan was performed to show the linearity in the lower dose region (0-15Gy) and R_2 measurement was made using the echo times of 57.5 to 360 ms with an interval of 22.5 ms.

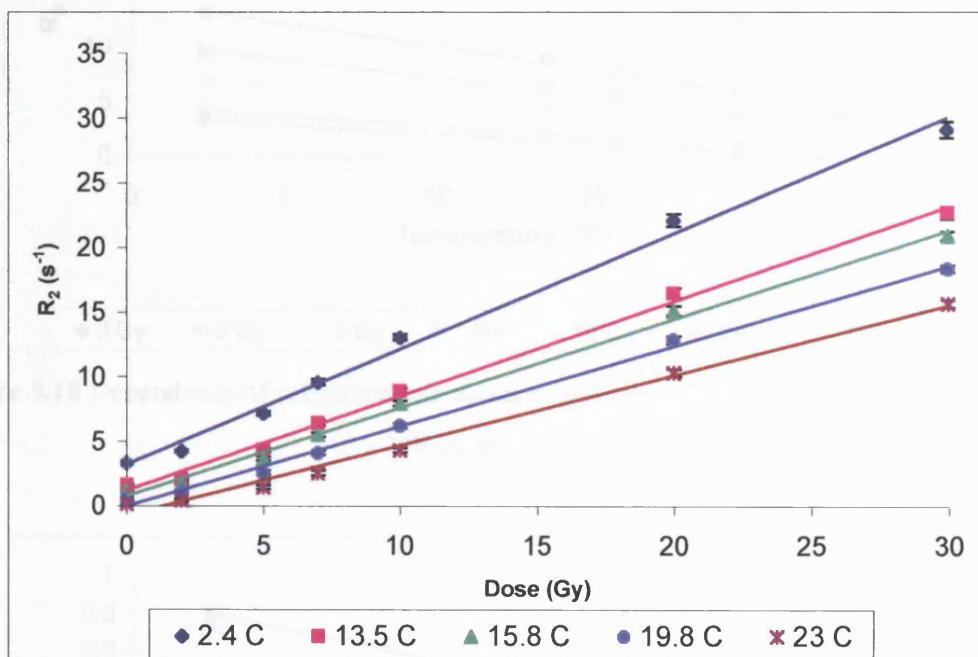


Figure 5.17a Dependence of relaxation rate R_2 on absorbed dose for different temperature during MR-acquisition.

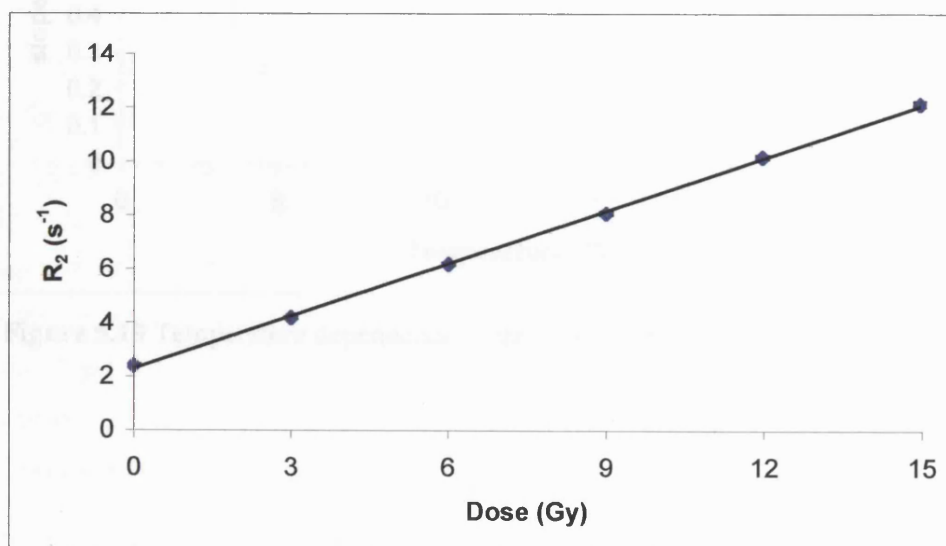


Figure 5.17b The linearity for 0-15Gy at room temperature.

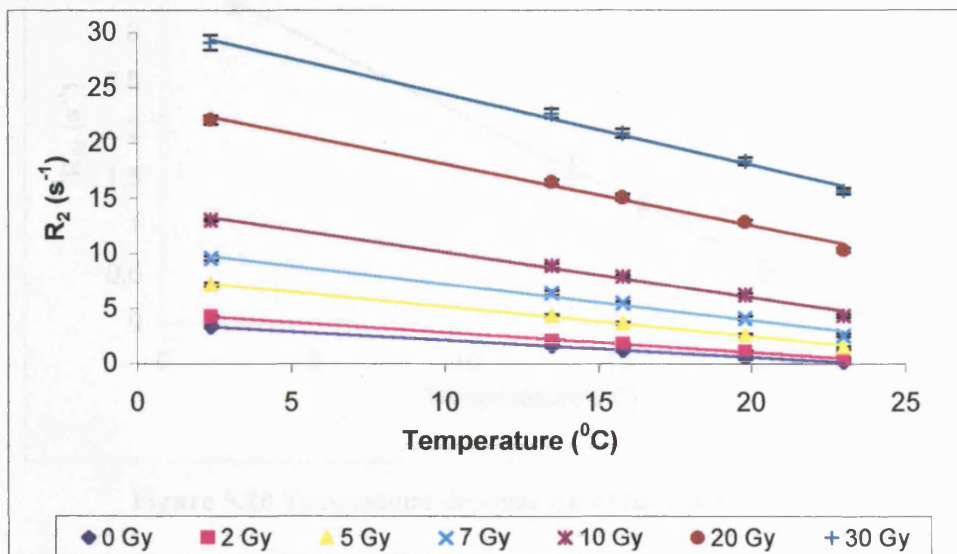


Figure 5.18 Dependence of relaxation rate R_2 on temperature for different dose level during MR-acquisition.

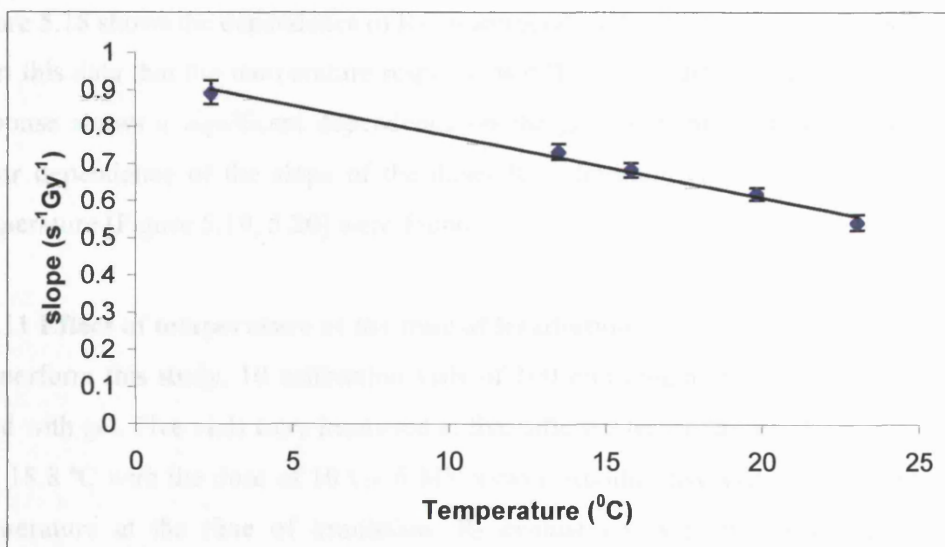


Figure 5.19 Temperature dependence of the slope of the R_2 versus dose curve

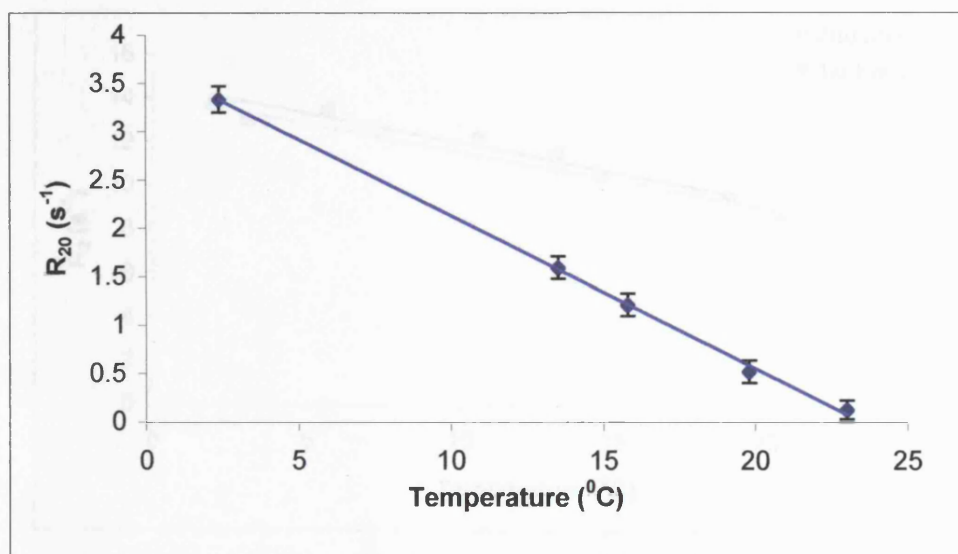


Figure 5.20 Temperature dependence of background R_2 curve.

Figure 5.17a shows dose response curves obtained from the MRI measurement performed at different temperatures from 2.4 °C to 23 °C. An expanded version of the dose response curve shows (figure 5.17b) the linearity of the lower dose region (0-15Gy) at room temperature. Figure 5.18 shows the dependence of R_2 on temperature for different dose levels. It is evident from this data that the temperature response is different for different dose levels. The dose response shows a significant dependence on the gel temperature during MR imaging. A linear dependence of the slope of the dose- R_2 calibration curve and background R_2 on temperature [Figure 5.19, 5.20] were found.

5.3.11 Effect of temperature at the time of irradiation

To perform this study, 10 calibration vials of 100 mm length and 25 outer diameter were filled with gel. Five vials were irradiated at five different temperatures of 2.0, 5.7, 10.6, 14.6 and 18.8 °C with the dose of 10 Gy 6 MV x-rays. Another five vials were used to measure temperature at the time of irradiation. R_2 evaluations were performed 24 hours after irradiation at room temperature. In a follow up experiment from another batch of gel, three gel vials were irradiated using 6 MV x-rays with the dose of 10 Gy at three different temperature of 3.1, 13.1, and 20.5 °C. For both studies, MR imaging was performed 1 day after irradiation at room temperature.

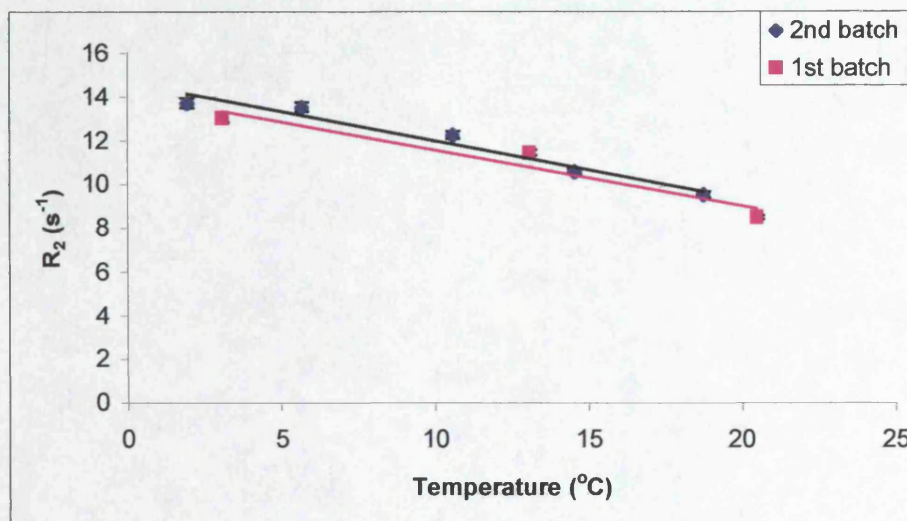


Figure 5.21 Effect of temperature at the time of irradiation on R_2 .

Figure 5.21 shows that the temperature at the time of irradiation has a significant effect on R_2 . R_2 decreases with increasing of temperature at a rate of $0.26 \pm 0.07 \text{ s}^{-1} \text{ per } ^\circ\text{C}$ for the 1st batch; $0.27 \pm 0.03 \text{ s}^{-1} \text{ per } ^\circ\text{C}$ for the 2nd batch. It can be seen that both batches show the same result.

6.3.12 Dose distributions

4 litres of gel were prepared for a head and neck phantom constructed from BarexTM [figure 5.22] to investigate the dose distributions resulting from a three field irradiation. Irradiation was performed 7 days after gel manufacture. The centre of the neck region was placed at the isocentre and the gel was irradiated using 6 MV x-rays with a field size of $6 \times 6 \text{ cm}$. The first irradiation was carried out with a plane beam; gantry angle was 0° and SSD was 95.7 cm. The second and third irradiation were performed with a 35° wedge beam with gantry angles of 90° and 270° and SSD of 94.7 and 94.6 cm. MR evaluations were performed 7 days after irradiation. A single spin echo sequence was used with in plane resolution of 0.75 mm with slice thickness of 3 mm.



Figure 5.22 Photograph of a head and neck phantom constructed using Barex™ sheet.

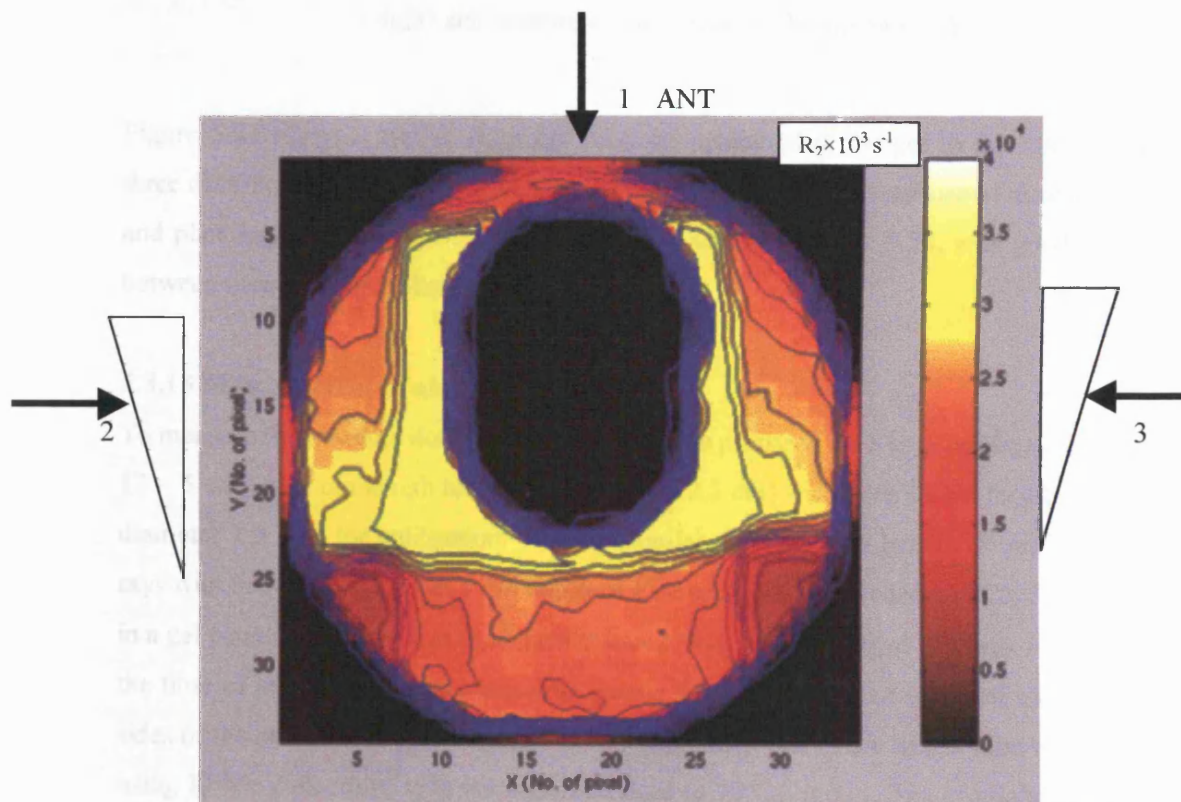


Figure 5.23 A typical R_2 distribution resulting from three field treatment using MAGIC gel in a Barex™ walled head and neck phantom (neck region). The difference in R_2 between successive contour levels is 2.85 s^{-1} . This figure was produced using Matlab. ✓

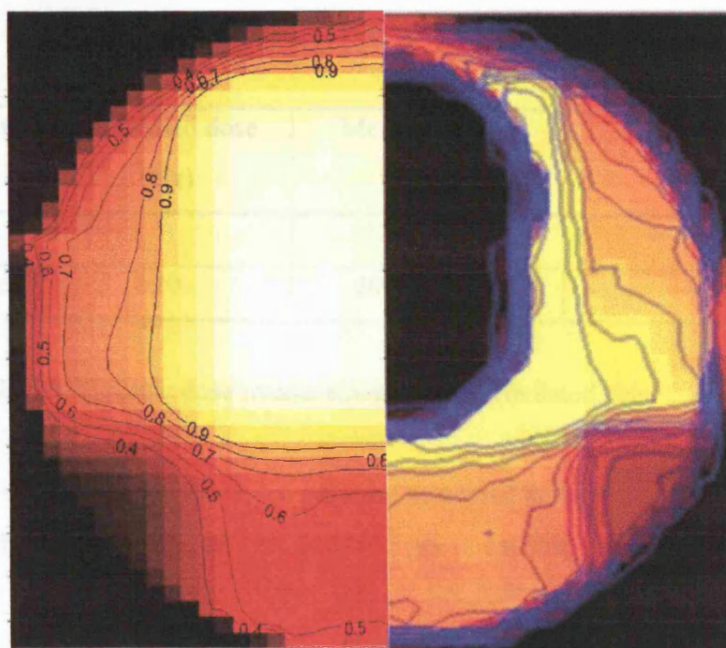


Figure 5.24 Qualitative comparison of three fields dose distributions between Magic gel (right) and treatment plan (PLATO-Nucleon)(left).

Figure 5.23 shows a typical dose distributions produced in the gel by the combination of three different 6MV x-rays beams. Qualitative comparison of the measured dose distribution and planning distribution (PLATO-Nucleon) is shown in figure 5.24, with good agreement between measured and planning distributions.

5.3.13 Measurement of absolute dose

To measure the absolute dose, 1.5 litres of gel were prepared for a rectangular phantom ($20 \times 12 \times 5$ cm), a 15 cm length tube (outer diameter 2.5 cm) and seven 10 cm length vials (outer diameter 2.5 cm) for calibration. The rectangular phantom was irradiated using 300 kV x-rays with the dose of 8 Gy at 5 cm depth of a Perspex phantom (equivalent to 5.95 cm depth in a gel phantom). The focus to surface distance was 50 cm and field size was 10×10 cm. At the time of irradiation tissue equivalent plastic sheets were placed top, bottom and on both sides of the phantom to get sufficient lateral scattering. The 15 cm length tube was irradiated using 12 MeV electrons with the absorbed dose of 20 Gy at $d_{\max}$. The irradiation set-up was described earlier (section 5.3.8). Seven calibration vials were irradiated using 6 MV x-rays with doses of 0, 3, 6, 9, 12, 15, and 20 Gy. MR measurement was performed 24 hours after irradiation. The temperature was almost the same for phantoms and all vials at the time of

irradiation and scanning. Dose images were produced using the method described in section 4.6.

Type of irradiation	Prescribed dose (Gy)	Measured dose (Gy)	Difference (%)
300 kV x-rays	8	7.73 ± 0.13	3.4
12 MeV electrons	20	20.02 ± 0.07	0.1

Table 5.5 Absolute dose measurements in the irradiated gels.

Table 5.5 shows the difference of up to 3.4% between measured and given dose. This result, when compared to table 4.10, suggests that MAGIC gel is capable of measuring absolute dose more accurately than PAG gel.

5.4 Discussion

Polymer gels have recently caused much interest in radiation therapy dosimetry and offer a wide range of potential applications in measuring three-dimensional dose distribution. In this work the MAGIC gel was manufactured using the formulation proposed by Fong et al [2001]. Initially, two types of gel were manufactured using HPLC water and de-ionised water. Gels made using HPLC water showed a better response than that made using de-ionised water. The dose response curve for the gel made with HPLC water showed linearity up to 50 Gy whereas gel from de-ionised water showed linearity up to 30 Gy. Therefore, HPLC grade water was used for the data presented in this chapter. Two types of methacrylic acid were used in this study: one is the product of Sigma (Product no.M0782), which has to be stored under the inert gas argon and another one is the product of Aldrich (Product No. 395374), which can be kept in a normal atmosphere. Gels made from the methacrylic acid from Aldrich was transparent, and did not show any polymerised area at the top of the phantoms or calibration vials. In contrast, methacrylic acid from Sigma gives rise to a slightly opaque gel, where the opacity occurs within two hours of manufacture in unirradiated gels. In the same type of gel, fogging was reported by Fong et al [2001] and an initial polymerisation takes place due to the creation of radicals from the ascorbate-copper-oxygen complex. The polymerised area at the top of the phantom or vials increases in size with time. It would appear that oxygen still plays a role in the gel. Another batch of gel was manufactured without hydroquinone, but had a higher background R_2 in comparison with that of the gels made with hydroquinone. This confirmed that hydroquinone has a significant

role in scavenging free radicals introduced from gelatin and other components, as suggested by Fong et al [2001]. Additional hydroquinone was also added to keep the monomer from auto-polymerisation before irradiation.

Post-manufacture, unirradiated gels show a continuous change in R_2 . The change of relaxation rate can be attributed to the initiation of polymerisation by the presence of free radical impurities in the gel components or by the creation of radicals from the ascorbate-copper-oxygen complex. These changes were seen to continue over the 8 week period of the study and would be expected to continue for a few months. Similar results were reported by McJury et al [1999a] and De Deene et al [2000a] for PAG gels and De Deene et al [2002a] for MAGIC gel.

The response of the gel to absorbed dose was found to linear up to 50 Gy. Using the same formulation, Fong et al [2001] reported linearity up to 30 Gy. In other studies, Gustavsson et al [2001] reported linearity up to 50 Gy, and De Deene et al [2002b] reported linearity up to 30 Gy. The slopes of the calibration curves were found to be in the range $0.60 \text{ s}^{-1}\text{Gy}^{-1}$ to $0.66 \text{ s}^{-1}\text{Gy}^{-1}$ and the intercepts within the range 3.0 s^{-1} to 5.2 s^{-1} for a 1T MRI scanner. Fong et al reported a slope of $0.68 \text{ s}^{-1}\text{Gy}^{-1}$ and $0.868 \text{ s}^{-1}\text{Gy}^{-1}$ and intercepts of 8.85 s^{-1} and 5.20 s^{-1} at 20 MHz ($\sim 0.5 \text{ T}$) and 85 MHz ($\sim 2.0 \text{ T}$) respectively. Gustavsson et al used MAGIC gel without hydroquinone and reported a slope of $0.41 \text{ s}^{-1}\text{Gy}^{-1}$ and $0.30 \text{ s}^{-1}\text{Gy}^{-1}$ and intercept of 3.20 s^{-1} and 2.12 s^{-1} measured with 0.25 T and 1.5 T MRI scanners respectively. In their study they used a multi spin echo sequence, in contrast to the single spin echo sequence that was used in our investigation. A multi spin echo sequence was also used in our experiments, and the slope and intercept were measured as $0.48 \text{ s}^{-1}\text{Gy}^{-1}$ and 2.81 s^{-1} respectively. For PAG gels, the relationship between absorbed dose and relaxation time was found to be linear up to about 10-12 Gy and the slope of the linear portion and intercept of the dose response curve have been reported as $0.34 \text{ s}^{-1}\text{Gy}^{-1}$ and approximately 1.45 s^{-1} respectively [Maryanski et al 1996, Farajollahi et al 1999]. In our study of PAG, slope and intercept were $0.22 \text{ s}^{-1} \text{ Gy}^{-1}$ to $0.37 \text{ s}^{-1}\text{Gy}^{-1}$ and 1.16 s^{-1} to 1.50 s^{-1} . It would appear that the linear range and dosimeter sensitivity for MAGIC gel is considerably greater than that for PAG.

In gel dosimetry, magnetic resonance imaging is used to determine changes in longitudinal and transverse relaxation rates, R_1 and R_2 respectively, which are related to absorbed dose by means of a calibration curve. A number of factors influence the uncertainty of the absorbed dose. These include accuracy of calibration curve [Oldham et al 1998b], ageing dynamics of

the polymer gel (Baldock et al 1999b, DeDeene et al 2000c, McJury et al 1999a), B_1 -field inhomogeneity [DeDeene et al 2000b] and eddy currents [DeDeene et al 2000a]. It has been shown by Baldock et al [2001] that the uncertainty in R_2 depends on the echo spacing. In this study a single-echo spin-echo sequence was used with echo times of 25, 50, 75 and 100 ms. In the spin echo sequence the signal produced after a 90° pulse can be refocused by a 180° pulse [Hahn 1950]. Echo times used in this study are enough to cover the exponential signal decay for the absorbed dose level of 10-50Gy. Echo times more than 100 ms were not used because no signals were observed at the higher dose level at these long echo times. An inherent problem with this technique when measuring T_2 values is the diffusion of spins, which occurs during the period between pulse application and echo formation in the medium. This gives rise to signal loss, particularly at long echo times. However for a multi-echo sequence, multiple 180° refocusing pulses are applied after the 90° pulse [Carr and Purcell 1954]. Inaccuracies in the 90° and 180° pulses propagate through the echo train, resulting in a complex combination of transverse magnetisation being lost to the longitudinal magnetization, thus resulting in a signal loss and stimulated echoes, originating from longitudinal magnetisation, giving rise to a signal increase in later echoes [Baustert et al 2000]. In this study the echo times were 22.5 to 360 ms for multi-spin echo sequence with an echo spacing of 22.5 ms. For R_2 measurements only echo times of 67.5, 90, 112.5, 135, 157.5 and 180 ms were used. The first two echo times were not used due to the pulse imperfections and last few ignored due to the low signal intensity at these long echo times. Ideally, there should be enough echoes to cover the exponential signal decay until it reaches the baseline or noise so that the majority of the decay is sampled. The echo times used here are enough to cover the exponential signal decay for the absorbed dose level of 10-50Gy. For both spin echo and multi spin echo sequences there is a decreased accuracy at the 0-10 Gy dose level. It has been found that the spin echo sequence yields better accuracy with a higher dose sensitivity compared to multi spin echo sequence. Conversely for multi spin echo sequence, the acquisition time is four times less than the single spin echo sequence. Figure 5.6 shows that the single echo sequence gives steeper slope, which should give a higher precision in dose in comparison with the multi-echo sequence. With long R_2 values in MAGIC gel, the advantage of a multi-echo sequence is not realised because long echo time images were discarded because of low signal intensity.

Two types of long-term instabilities were observed. One is the effect of the time from manufacture to irradiation on the slope of the dose- R_2 plot and other is the effect of the time from irradiation to scanning on the slope of the dose- R_2 plot. The gel shows very consistent

response from 1 day to 14 days after manufacture. There is excellent linearity of response with dose and an ability to be stored for at least 14 days before use. It has been reported by McJury et al [1999a] that the polymerisation reactions for PAG continues post-irradiation for many weeks; in contrast, De Deene et al [2000a] reported that post-irradiation polymerisation lasts only 12 hours after irradiation. In another study, it was reported by De Deene et al [2002a] that the R_2 -dose sensitivity increases with time for PAG and decreases for normoxic gels. In the present study it was found that the post-irradiation polymerisation becomes stable 1 day after irradiation and remains stable for at least 8 weeks after irradiation. The slope of the dose response curve up to 50 Gy was found to be stable within $\pm 5\%$ over the period from 1 day to 8 weeks post irradiation. This variation may be due to temperature differences at the time of scanning, although all vials were left in the MRI scanning room before imaging for 24 hours to equilibrate to room temperature. However, during another study [section 5.3.7], room temperature variation was recorded as $\pm 2^\circ\text{C}$ from one day to another, with dose response decreasing by $0.017\text{s}^{-1}\text{Gy}^{-1}$ per $^\circ\text{C}$ [section 5.3.10]. In contrast, De Deene et al [2002a] reported that the response of the MAGIC gel decreases with time. This difference might be due to the temperature control at the time of manufacture; furthermore in this study HPLC water was used, whereas deionised water was used by De Deene et al [2002a]. The optimum time to image the dosimeter post-irradiation would be when a steady state has been reached, with all polymerisation reactions completed and thus maximum sensitivity having been achieved. Imaging should therefore be performed a minimum of approximately 1 day post-irradiation to achieve a maximum sensitivity of the dosimeter.

It has been reported by Maryanski et al [1994] and Bonnett et al [1999] that radiation induced polymerisation is inhibited at the surface of plastic vessels (polystyrene, Lucite, polycarbonate, PVC and Perspex) for PAG gel. It has been also reported by Bonnett et al [1999] that this effect increases with time after manufacture, and that even Barex exhibits the inhibition of polymerisation within a few mm of the phantom wall. It has been reported by both authors that this effect is not present when glass vessels are used. In the present study, it was found that the response of the MAGIC gel was unaffected by the material used for the walls of the container, unlike other polyacrylamide gels. This response is stable at least up to 7 days after manufacture. It should be noted that the beam profile in each phantom shows lower dose at the surface. This is most likely to be due to small air bubbles at the surface.

It has been reported by Maryanski et al [1994] and De Deene et al [2001] that dose overestimation has been observed in PAG gel when irradiated at high doses, and that this

effect can be attributed to long-lived polymer radicals. In the present study, increased dose was observed at the edge of the irradiated area 1 day after irradiation [Figure 5.11] and this value increased with time. The dose increase was possibly due to a contribution from polymer originating from the fresh monomers in the un-irradiated regions migrating to the edge of the irradiated region and reacting with long-living polymer radicals in the irradiated regions. In a study using x-ray CT for the measure of PAG gel Trapp et al [2002] reported that the density increase in an irradiated polymer gel dosimeter is related to a volume decrease. They also reported that the volume decrease implies that there will be some spatial change within the gel. On the basis of their results it can be said that volume of the irradiated portion may also decrease with time in this case. However, the narrowing of the estimated irradiated region over time is still a confusing finding, and demands further investigation.

The BANG™ gel dose response is independent of energy for a range of commonly used electron and photon energies as reported by several authors [De Wagter et al 1996, Ibbott et al 1997, Farajollahi et al 1999, Baldock et al 1996d]. Energy independence for BANG™-2 polymer gel dosimeter was reported by Maryanski et al [1996], Conversely an energy dependence for BANG-2 polymer gel dosimeter was reported by Novotny Jr et al [2001]. Ramm et al [2000] irradiated polymer gel phantoms with monoenergetic ^{12}C ion beams in the energy range between 135 MeV u^{-1} to 410 MeV u^{-1} . They concluded that the efficiency of polymer gel with heavy ion irradiation is strongly dependent on the linear energy transfer and projectile energy. It was reported by Jirasek et al [2002] that gel response decreases when irradiated with protons as compared with the x-ray response. The present study of the dose response of MAGIC polymer gel dosimeter as a function of beam energy demonstrated that the gel dose response shows negligible energy dependence in the range of 6 to 12 MeV electrons. The lower accuracy was observed at 0-10 Gy dose region due to the selection of echo times, but otherwise it shows significantly the same results. Ideally, there should be enough echoes to cover the exponential signal decay until it reaches the baseline. The echo times used in this study were not enough to cover the exponential signal decay for the absorbed dose below 10Gy. Measured electron energies using MAGIC gel show good agreement with ionisation chamber measurements. Small variations were observed for the measurement using radiochromic HD 810 film. This difference may be due to the reading error. The densitometer evaluated the density to only two decimal places and it may therefore be possible that the densitometer is not sufficiently sensitive to detect small variation in response with energy. For ionisation chamber measurements it is difficult to place a chamber

at an exact depth. From the above discussion it can be said that MAGIC gel response shows negligible energy dependence at least up to 12 MeV electron energy.

The slope of the dose response for the MAGIC gel varies with the temperature of the gel during MR measurements; therefore special attention must be paid to gel temperature during the MR measurement to avoid miss-interpretation of the results. In the present study, the decrease in slope was found to be $0.017 \text{ s}^{-1}\text{Gy}^{-1}\text{per } ^\circ\text{C}$. The temperature dependence of the PAG dosimeter has been studied by Maryanski et al [1994, 1995b, 1997a] and De Deene et al [1998]. They found a reductions of slope of $0.01 \text{ s}^{-1}\text{Gy}^{-1}\text{per } ^\circ\text{C}$ [Maryanski et al 1995b, 1997a] and $6.3 \times 10^{-3} \text{ s}^{-1}\text{Gy}^{-1}\text{per } ^\circ\text{C}$ [DeDeene et al 1998]. Thus MAGIC gel has a significantly greater temperature dependence than PAG gel. The effect on R_2 at the time of irradiation was also evaluated, although Maryanski et al [1995b] reported that at the time of irradiation BANG™ gel has no significant effect. In the present study, it was found that R_2 decreases around $0.268 \text{ s}^{-1} \text{ per } ^\circ\text{C}$. Temperature changes during irradiation are not insignificant (up to $12 \text{ }^\circ\text{C}$ being observed) [Salomons et al 2002]. The different physical properties of the PAG and MAGIC gels (amount of heat generated, thermal conductivity, heat capacity) may give very different thermal properties during irradiation, leading to different degrees of polymerisation according to the local temperature. ✓

Using the MAGIC gel it is possible to get the dose distribution with adequate accuracy and the absolute dose with around 3.4% accuracy. MacDougall et al [2002] reviewed the accuracy of several authors and reported that the accuracy range is 8 to 23.5% for PAG gel, which is significantly greater than the result obtained here for MAGIC gel.

These investigations show here firm evidence that the MAGIC gel dosimeters can be produced with adequate sensitivity, reproducibility and accuracy. Magic gel is more convenient to manufacture, and has no energy dependence. It has also been demonstrated that it can be used in real dosimeters. The sensitivity, stability, and linearity are significantly better than PAG.

Chapter 6

The application of PAG in endovascular brachytherapy

6.1 Introduction

In brachytherapy the irradiated tissue is always close to or in contact with the radiation sources, and the effect of the inverse-square law results in steep dose gradients within the tissues. It is necessary to measure the dose distribution with a resolution of the order of less than 1 mm because of the steep dose gradient, and there is a need to measure in three dimensions around complex geometries. For intravascular brachytherapy with catheter-based systems, AAPM Task Group 60 [Nath et al 1999] recommended that the dose rate should be measured at a reference point located at a radial distance of 2 mm from the centre of the catheter, the dose rate at that distance should be uniform to within $\pm 10\%$ over the central two thirds of the treated length, and the relative dose rate in the plane perpendicular to the catheter axis through the centre of the source should be measured at distances from the centre ranging from 0.5 mm to the distance where the 90% of the energy from a point source is absorbed at intervals of 0.5 mm. It is difficult to measure absorbed dose using conventional dosimeters. In trying to measure doses in close proximity to the source with an ion chamber, the physical size of the chamber will seriously disturb the radiation field and introduce errors into the reading; furthermore it does not have sufficient spatial resolution. LiF TLD crystals with a physical size of $3.5 \times 3.5 \times 0.35 \text{ mm}^3$ have better spatial resolution, but it can be difficult to position the dosimeter accurately to measure the dose in vascular brachytherapy. The three dimensional dose distribution could be measured by using TLDs, but this would be quite time consuming. Similarly, the distribution could not be measured with diodes, because of the difficulty in accurate spatial positioning and also their energy dependence. Film dosimetry offers high spatial resolution but it is difficult to manipulate in a complex geometry, it is not tissue equivalent and its response is energy dependent. GAF-Chromic film is one method that has been used for the dosimetry of vascular brachytherapy sources [Pai et al 1998, Steidley et al 1998, Soares et al 1998], but it is restricted to measurements in two dimensions, as are measurements with scintillator devices [Bambynek et al 2000].

Fricke gel is able to give three dimensional dose mapping and is also suitable for both high dose rate (HDR) [Olsen and Hellesnes 1994, Schreiner et al 1994] and low dose rate (LDR)

brachytherapy [Olsen and Hellesnes 1994]. However, there is a gradual blurring of the radiation dose pattern with time due to the diffusion of the radiation-induced chemical changes (conversion of ferrous to ferric ions) [Day 1990, Balcom et al 1995, Harris et al 1996]. Polymer gel dosimetry, which has been used for measurements of more conventional brachytherapy sources [e.g., Maryanski et al 1994, 1996, Farajollahi et al 1999, Ibbott et al 1999, McJury et al 1999b], does not suffer the diffusion problem. Using a polyacrylamide gel (PAG) as a dosimeter has the advantages that the distributions can be measured in three dimensions, the gel is both dosimeter and phantom, and the gel is tissue equivalent. To date, in-plane resolution for the dose distributions from gel dosimeters has been reported as being typically 0.14 mm to 1.5 mm for MRI [e.g. De Deene et al 1998, Farajollahi et al 1999, Häfeli et al 2000, Ertl et al 2000, Berg et al 2001] and 2 mm for a prototype scanner for optical tomography [Gore et al 1996]. More recent work describing optical scanners indicates that spatial resolution better than 1 mm³ is achievable [Doran et al 2001a, Oldham et al 2001]. The spatial resolution achievable in MRI is ultimately determined by the strength of the magnetic field gradient used for imaging. However, the signal-to-noise ratio (SNR) depends inversely on the third power of the spatial resolution, so the resolution that is achievable in practice is limited by SNR, and depends on the strength of the magnetic field (B_0), and on the time available for scanning [Edelstein et al 1983]. Using a high-field MRI system, the resolution achievable may be sufficient for the needs of vascular brachytherapy dosimetry.

In this chapter the results of measurements of depth dose distributions and dose profiles parallel and orthogonal to the source axis for a ⁹⁰Sr/⁹⁰Y source train using polymer gel dosimetry with high field high resolution MRI are presented and discussed. These results have been compared with the dose distributions measured using MD-55 and HD-810 radio chromic film. Absolute doses have also been measured using the polymer gel and have been compared the results using radio chromic film and these are also discussed. The dose response of the gel at two field strengths, 1.0 and 4.7 Tesla has also been compared.

The depth dose data for a curved coronary artery phantom and a bifurcation phantom were measured. Profiles parallel to the source axis for a phantom with a metallic stent were also measured.

6.2 Materials and Methods

6.2.1 Sources

The radiation source used in this investigation was a high dose rate $^{90}\text{Sr}/^{90}\text{Y}$ source train from a Betacath™ device (Novoste) (Figure 6.1). The source consisted of a train of 16 $^{90}\text{Sr}/^{90}\text{Y}$ pellets encapsulated in a strontium titanate ceramic. $^{90}\text{Sr}/^{90}\text{Y}$ is a high beta emitter with maximum beta energy of 2.28 MeV. The outer diameter of each pellet was 0.65 mm with a length of 2.5 mm. The sources were transported hydraulically from the source container in the Betacath™ using a catheter of 1.6 mm diameter with three lumen: one for the sources, one for the return fluid, and one for the guide wire. A syringe filled with sterile water drove the hydraulic delivery system.

6.2.2 Gel preparation and irradiation

The polymer gels employed in this study were prepared using the method described in chapter 4.4. The composition of the polymer gel used was 5% gelatin, 3.5% acrylamide and 3.5% N, N'-methylene-bis-acrylamide by weight.

The calibration vials used in the study were glass tubes 100 mm long and 25 mm outer diameter and the phantoms were 143 mm long and 28 mm outer diameter for glass insert and 150 mm long and 25 mm outer diameter for barex insert. The brachytherapy phantoms had either an insert of Barex™ with a 2 mm inner diameter and 4 mm outer diameter, or a glass insert with a 2 mm inner diameter and 3 mm outer diameter. Both types were closed at one end.

This insert tube was positioned along the central axis of the glass tube, and held in position with a rubber stopper as shown in figure 6.2. This initial design of phantom was limited by the inability of the rubber stopper to keep the insert supported centrally in the glass tube and difficulties were experienced in manufacturing Barex™ inserts from sheet material. An improved design of phantom was also constructed using a glass tube with glass thickness of 0.5 mm. This tube was also closed at one end and sealed with quartz quick-fit stopper.

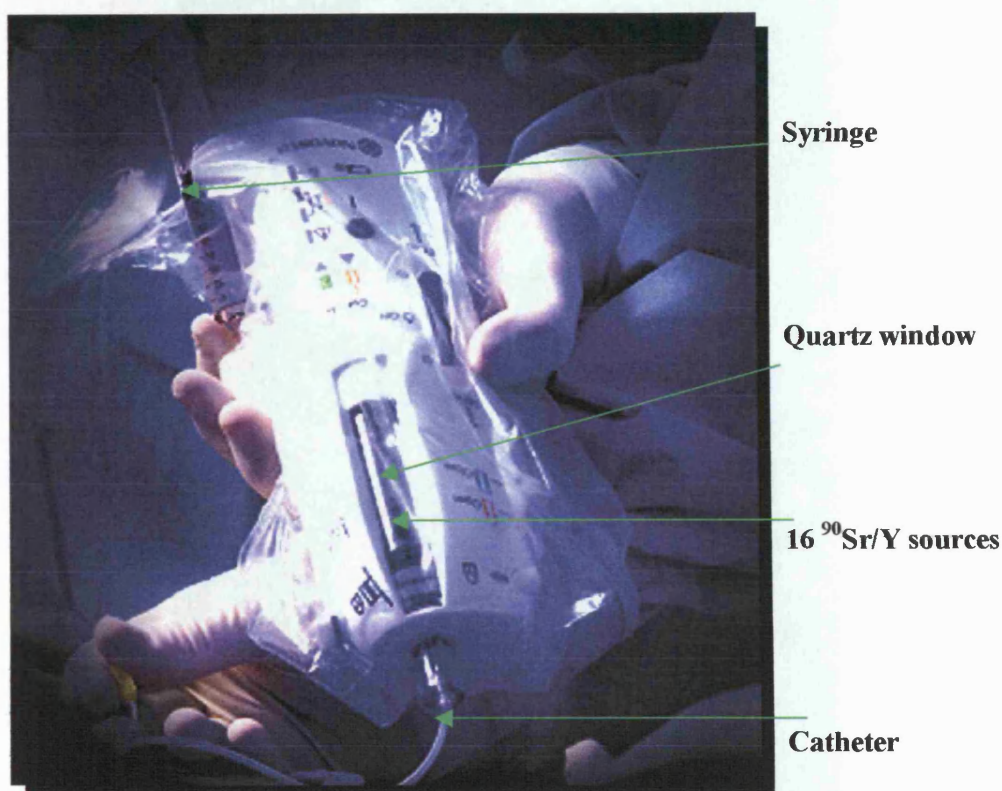


Figure 6.1 Photograph of Novoste Betacath™ device.

Barex™ has the advantage of being nominally tissue equivalent, while glass is more rigid but may perturb the beta radiation. Another phantom was made which simulated a curved coronary artery. For this phantom, a glass tube 115 mm long with 2 mm inner and 3 mm outer diameter was bent through an angle of 100° (angle of arc). The tube was inserted in a rectangular Barex™ phantom measuring $40 \times 40 \times 125$ mm [figure 6.3]. In order to investigate the dose distribution of $^{90}\text{Sr}/^{90}\text{Y}$ vascular brachytherapy sources with stent a specially designed phantom was constructed as figure 6.4. It had two parts: one part was constructed using Barex™ [rectangular shaped $40 \times 40 \times 125$ mm] and filled with gel, another part was made from a Perspex sheet of $10 \times 40 \times 120$ mm. The catheter and stent could be sandwiched between them. Finally, a coronary artery phantom for studying the effects of radiation in bifurcated arteries (60°) was constructed [Figure 6.5]. The dimensions of the bifurcation tube were 4 mm outer diameter and 2 mm inner diameter.

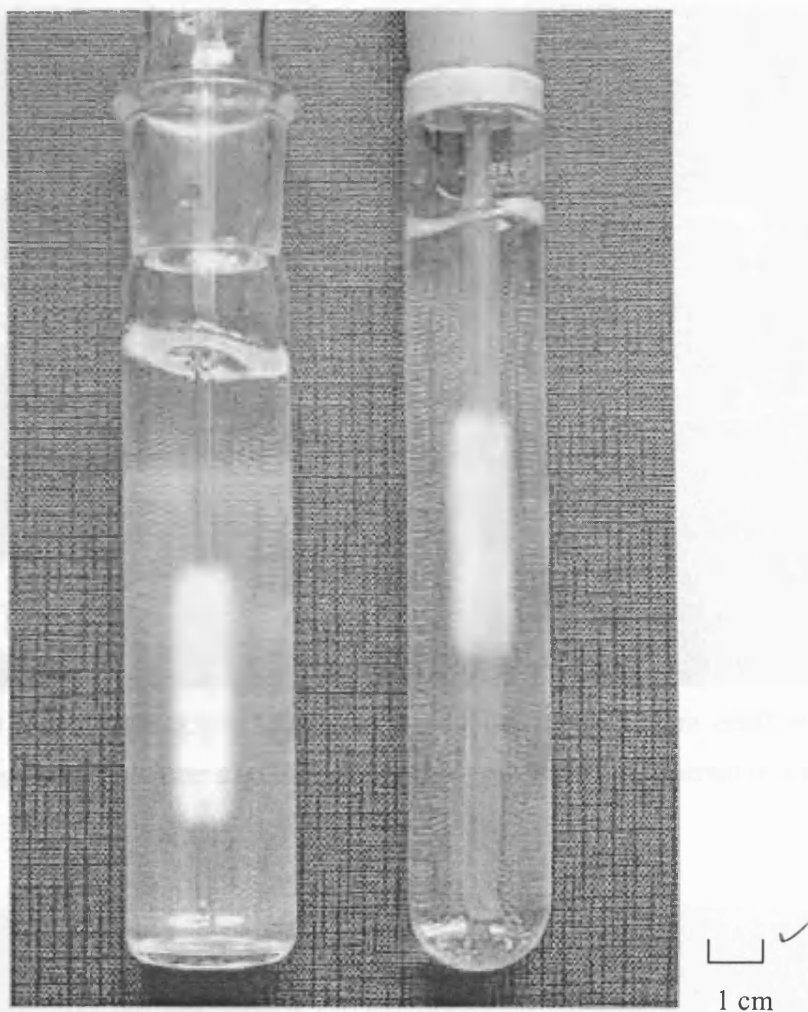


Figure 6.2 Cardiovascular phantom of glass (left) and Barex™ (right) insert after irradiation of 8 Gy $^{90}\text{Sr}/^{90}\text{Y}$.

Calibration vials were irradiated to doses of 1, 2, 4, 6, and 8 Gy using a 6 MV photon beam with a 15×15 cm field. The calibration tubes were irradiated 5 cm deep in a Perspex holder [figure 4.7] and were rotated through 180° halfway through the irradiation to give a uniform dose distribution. The phantoms were irradiated using $^{90}\text{Sr}/^{90}\text{Y}$ sources to doses of 8 and 10 Gy at 2 mm radial distance from the source centre. The absorbed doses were calculated using source calibration data traceable to NIST (USA) and supplied with the sources.

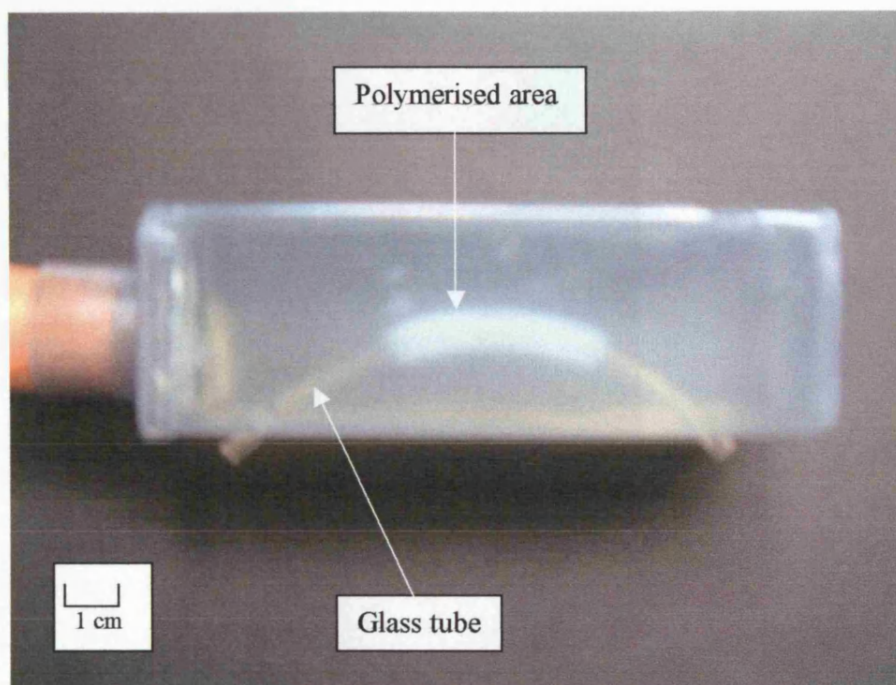


Figure 6.3 Cardiovascular curved phantom. A bent glass tube (115 mm length with 2 mm inner diameter and 3 mm outer diameter, and angle of arc 100°) was inserted in a rectangular BarexTM phantom.

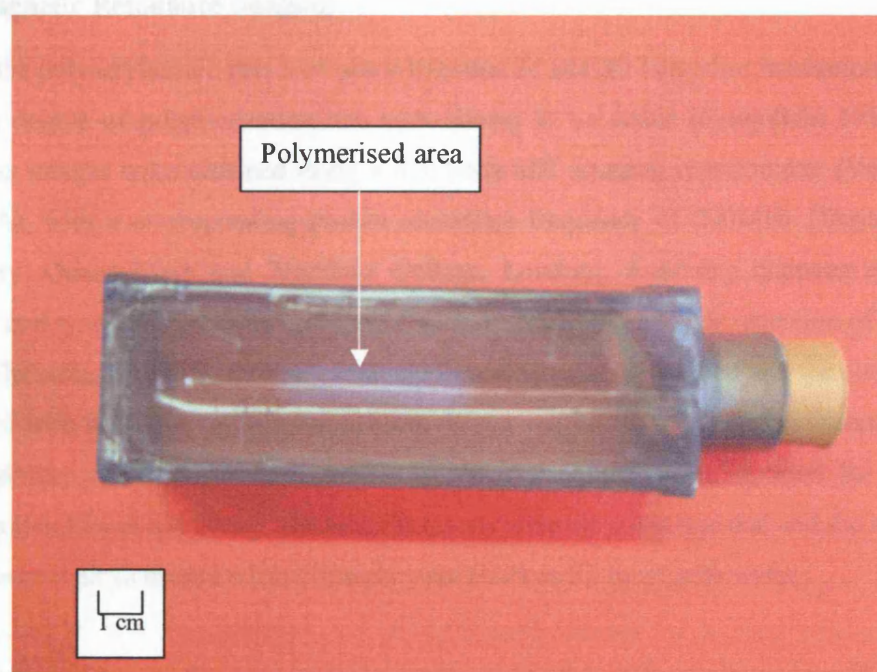


Figure 6.4 Cardiovascular stent phantom.

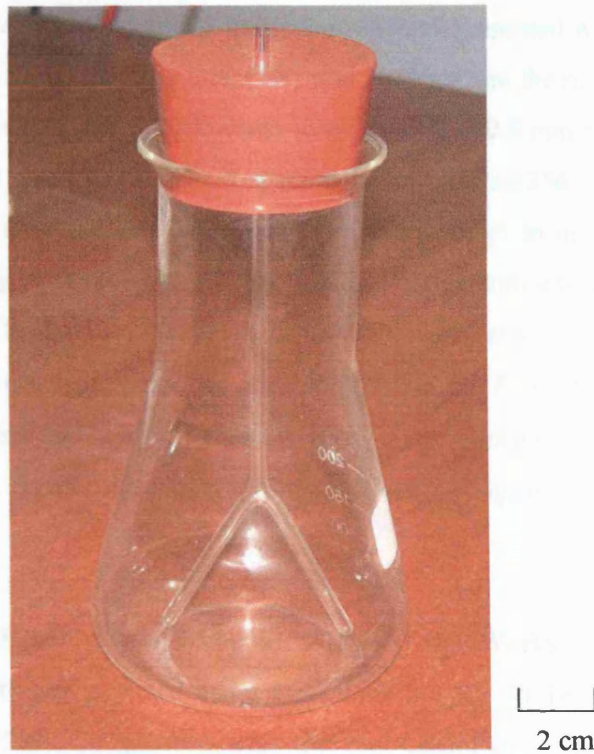


Figure 6.5 Cardiovascular bifurcation phantom.

6.2.3 Magnetic Resonance Imaging

MRI of the polyacrylamide gels took place between 20 and 30 days after irradiation, at which time the degree of polymerization has been shown to be stable [Farajollahi 1998]. High-resolution images were obtained using a 4.7 Tesla MR imaging spectrometer (Varian, Palo Alto, CA), with a corresponding proton resonance frequency of 200MHz [Department of Chemistry, Queen Mary and Westfield College, London]. A 60 mm diameter quadrature receiver coil was used for radio frequency pulse transmission, and for reception of the NMR signal. The straight inserts that had contained the catheter were air filled and the curved insert was filled with water for the imaging process. Water was added to the curved insert to reduce the possibility of magnetic susceptibility artefacts that have been reported for air filled catheters [McJury et al 1999b]. The straight inserts were closed at one end and the small bore did not permit air to escape when attempts were made to fill them with water.

MRI measurements of the transverse relaxation rate (R_2) of the polyacrylamide gels took place between 20 and 30 days after irradiation, at which time the degree of polymerization has been shown to be stable [Farajollahi et al 1998]. This time was longer than usually used and was governed by the availability of the spectrometer. MRI scanning was performed at

room temperature using a single echo spin-echo sequence, repeated with echo times (TE) of 25, 150 and 300 ms. The repetition time (TR) was 3000 ms and the in-plane image resolution was either 0.2 or 0.4 mm. Slice thicknesses were 1 mm and 0.5 mm for the 0.4 and 0.2 mm in-plane resolutions respectively. The k -space data matrix was 256 x 256 in all cases, and data were acquired at least twice and signal averaged in order to improve the SNR, and to enable phase cycling of the RF pulses, thus reducing image artefacts. Imaging times were of the order of 1 hour for 0.4 mm resolution, while for 0.2 mm resolution, imaging times of 10 hours were used in order to reduce the standard error in the R_2 readings to less than $\pm 3\%$. The MRI images were transferred to a Sun Microsystems workstation (Palo Alto, CA, USA) for further analysis. R_2 and dose images were produced using the formulation described in section 4.6.

Isodose distributions were drawn using MATLAB (Math Works Inc., Natick, MA). The calibration vials were also scanned using a Siemens Impact 1.0 Tesla whole body scanner (Siemens, Germany) for comparison with the high-resolution results. A multi-spin-echo sequence was used with 16 echo times from 50 to 800 ms of interval 50 ms and a TR of 3000 ms with a field of view of 192 mm.

6.2.4 Radiochromic film dosimetry

Two types of film were used for film dosimetry. The first type is known as HD-810 (Nuclear Associates) and consists of a single layer of radiation sensitive emulsion, approximately 7 microns thick, on a 0.22 mm polyester base. The second type of film is known as MD-55 (Nuclear Associates). This is a laminated film composed of two pieces of 0.27 mm polyester base, each with a nominal 15 micron thick coating. Recommendations on the use of radiochromic film have been given in the literature [Niroomand-Rad et al 1998]. One of the major advantages of the radiochromic film in comparison with radiographic film is that this film does not need to be developed. The films were read with a manual Radiochromic Densitometer (Model 37-443, Nuclear Associates) with an ultra bright LED light source with a peak wavelength of 660 nm. To improve the resolution of this device, the aperture of 2 mm was reduced to approximately 0.3 mm using a small annular insert. The calibration curve (optical density vs. absorbed dose) was determined between 0 and 32 Gy for the double layer and between 0 and 32 Gy for the single layer film after irradiating with 6 MV x-rays. A solid, water equivalent phantom [WTe, St Bartholomew's Hospital London] was designed for irradiating the film using a $^{90}\text{Sr}/^{90}\text{Y}$ source and is shown in figure 6.6. The rectangular

phantom was constructed in two halves [overall dimensions 38 mm × 38 mm × 50 mm] with a 1.8 mm hole drilled down the central axis of the phantom into which the catheter was inserted. For each film type, two 20 mm × 60 mm pieces of film were carefully placed on either side of the central hole. The MD-55 film was exposed using 20 Gy and the HD-810 was exposed using 32.2 Gy. All films were read 24 hours after exposure. The AAPM recommendations for radiochromic film dosimetry were followed [Niroomand-Rad et al 1998].

In order to investigate the energy dependence of GAF chromic film, the same batch of both types of film were exposed to a range of the following energies [table 6.1]. Before irradiating the film, the output of each machine was calibrated using appropriate chambers and their associated traceable calibration factors. The film was then left at least 24 hours before being read out. In each case a background reading from a sample of un-irradiated film was subtracted from the readings. It should be noted that this calibration was not carried out by myself but by other members of the department [M. Poulton and D. Bonnett].

Machine	Type of radiation	Nominal energy (E_0)
Pantak 300	Photon	300kV
Philip Sli	Photon	6 MV
Philip Sli	Electron	4 MeV (3.48 MeV)
Betatron CMB10	Electron	1.3 MeV (0.95 MeV)
Betatron CMB10	Electron	2.4 MeV (1.55 MeV)
Betatron CMB10	Electron	3.8 MeV (2.54 MeV)

Table 6.1 Source of radiation with output energy used in this experiment with type of radiation.

6.3 Results

Figure 6.7 shows a photograph of the polymerised area of the gel phantom for both glass and Barex™ inserts. A dose image was produced using the 1 T MRI scanner for the Barex™ insert phantom, and is shown in figure 6.8. Another transverse relaxation rate (R_2) image from the 4.7 T scanner in a transverse plane is shown in figure 6.9.

In order to demonstrate the three-dimensional nature of the dose measurement, a longitudinal view was also produced (figure 6.10). An R_2 image of the curved phantom, stent phantom and bifurcation phantom (60°) is also shown in figure 6.11. There was no evidence of artefacts due to magnetic susceptibility variations within the phantom for either the straight insert, which could not be filled with water, or for the curved insert, which was water-filled. If susceptibility artefacts had occurred they would have been seen at the air/material (glass or BarexTM) interface, which would not affect any measurements, made 2 mm or more from the source centre. Figure 6.12 shows the irradiated MD 55 film for 20 Gy and HD 810 film for 100 Gy.

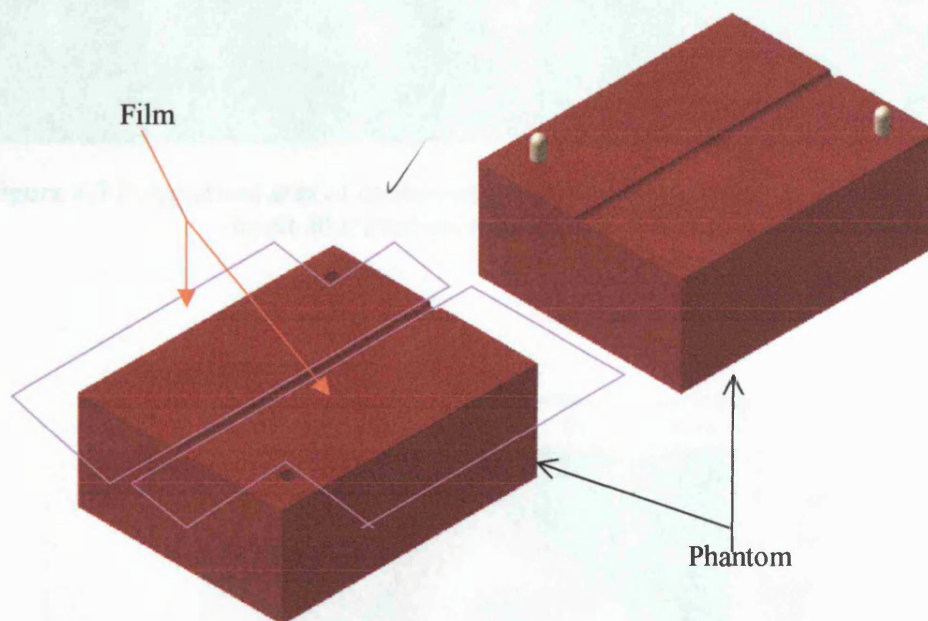


Figure 6.6 Solid water equivalent phantom for measuring dose using radio chromic film. The two halves sandwich two pieces of film, one either side of the central hole, into which the source is inserted.

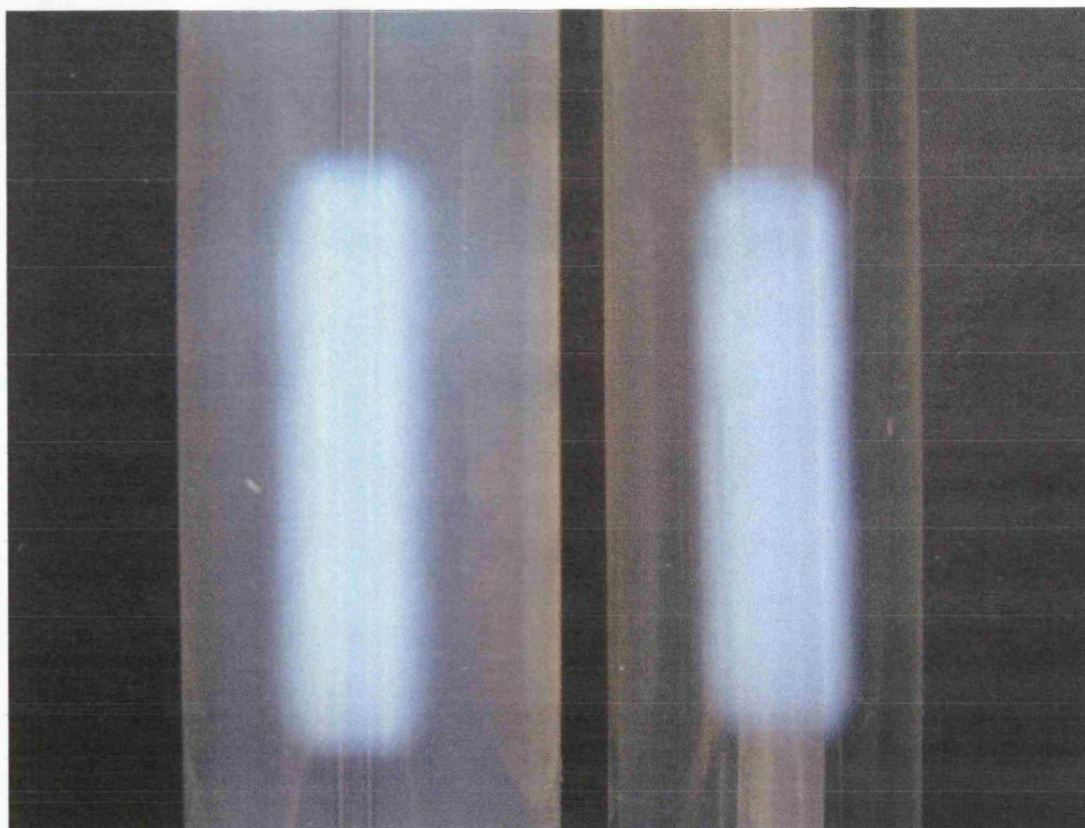
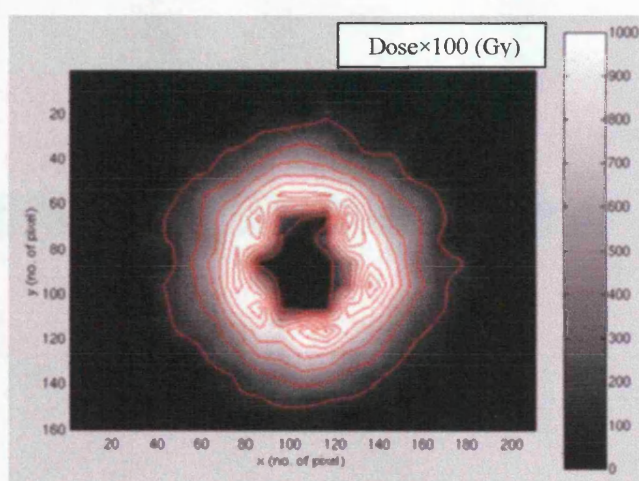


Figure 6.7 Polymerised area of cardiovascular phantoms with glass (left) and Barex™ (right) insert after irradiation with 8 Gy $^{90}\text{Sr}/^{90}\text{Y}$ sources.



b

Figure 6.8 Dose map of polymer gel used as a vascular brachytherapy phantom and irradiated by the ^{90}Sr sources with an in-plane resolution of 0.75 mm, acquired using a 1.0 T scanner.

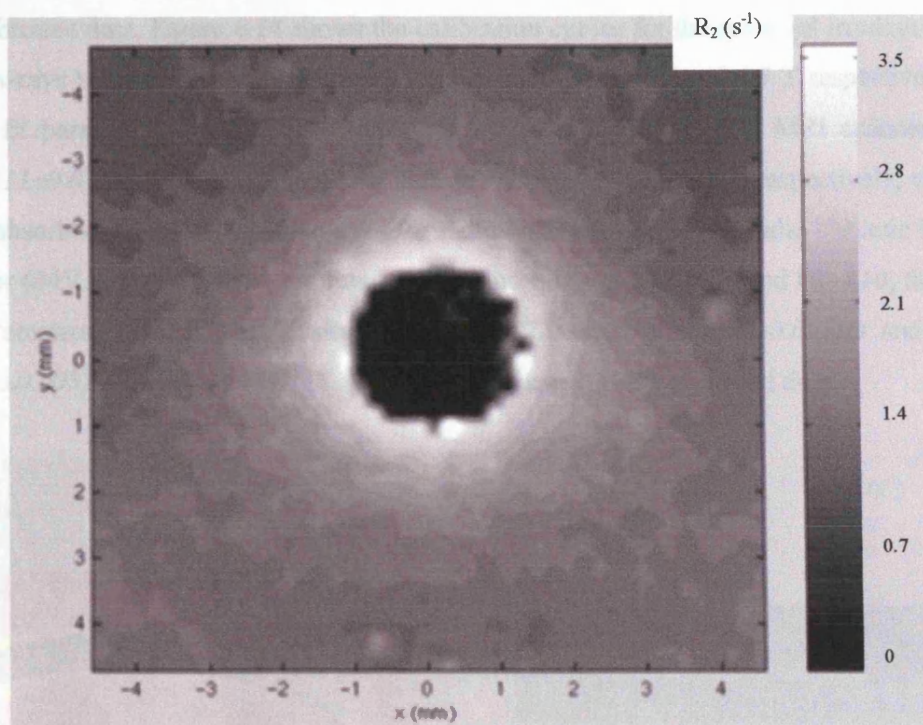


Figure 6.9 Transverse R_2 image of PAG used as a vascular brachytherapy phantom and irradiated using $^{90}\text{Sr}/^{90}\text{Y}$ sources with an in-plane resolution of 0.2mm.

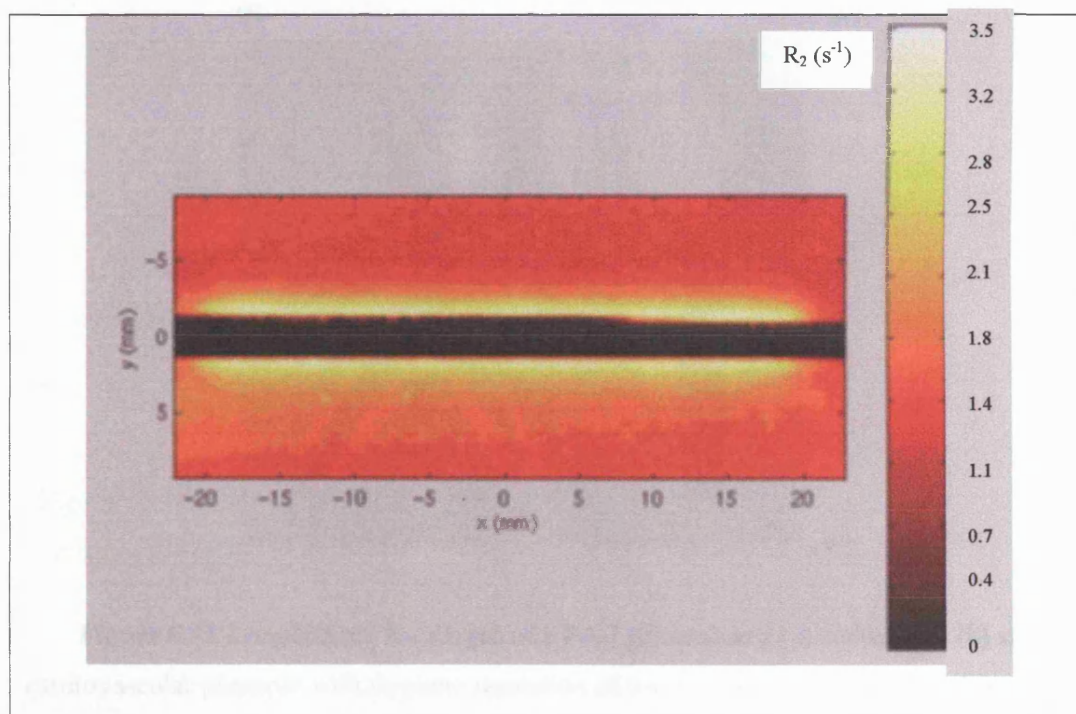


Figure 6.10 Longitudinal R_2 image of PAG used as a straight vascular brachytherapy phantom and irradiated using $^{90}\text{Sr}/^{90}\text{Y}$ sources with 0.2mm in-plane resolution.

Figure 6.13 shows the initial depth dose data from the 1 T MRI scanner and compares it with radiochromic data. Figure 6.14 shows the calibration curves for the same gel irradiated using 6MV x-rays but scanned using different field strengths of 1.0 T and 4.7 T respectively. The linear fit parameters of the calibration data for the 1.0 T and 4.7 T MRI scanners were $R_2 = (1.11 \pm 0.04) + (0.28 \pm 0.01)D$ and $R_2 = (1.53 \pm 0.07) + (0.28 \pm 0.01)D$ respectively, where D is the absorbed dose. Calibration curves for radio chromic MD 55 and radio chromic HD 810 film for 6MV x-rays are shown in Figure 6.15a and 6.15b. For MD 55 and HD 810, the linear fit parameters were optical density (OD) = $(0.014 \pm 0.01) + (0.046 \pm 0.001)D$ and $OD = (0.004 \pm 0.005) + (0.009 \pm 0.0002)D$ respectively, where D is the absorbed dose.

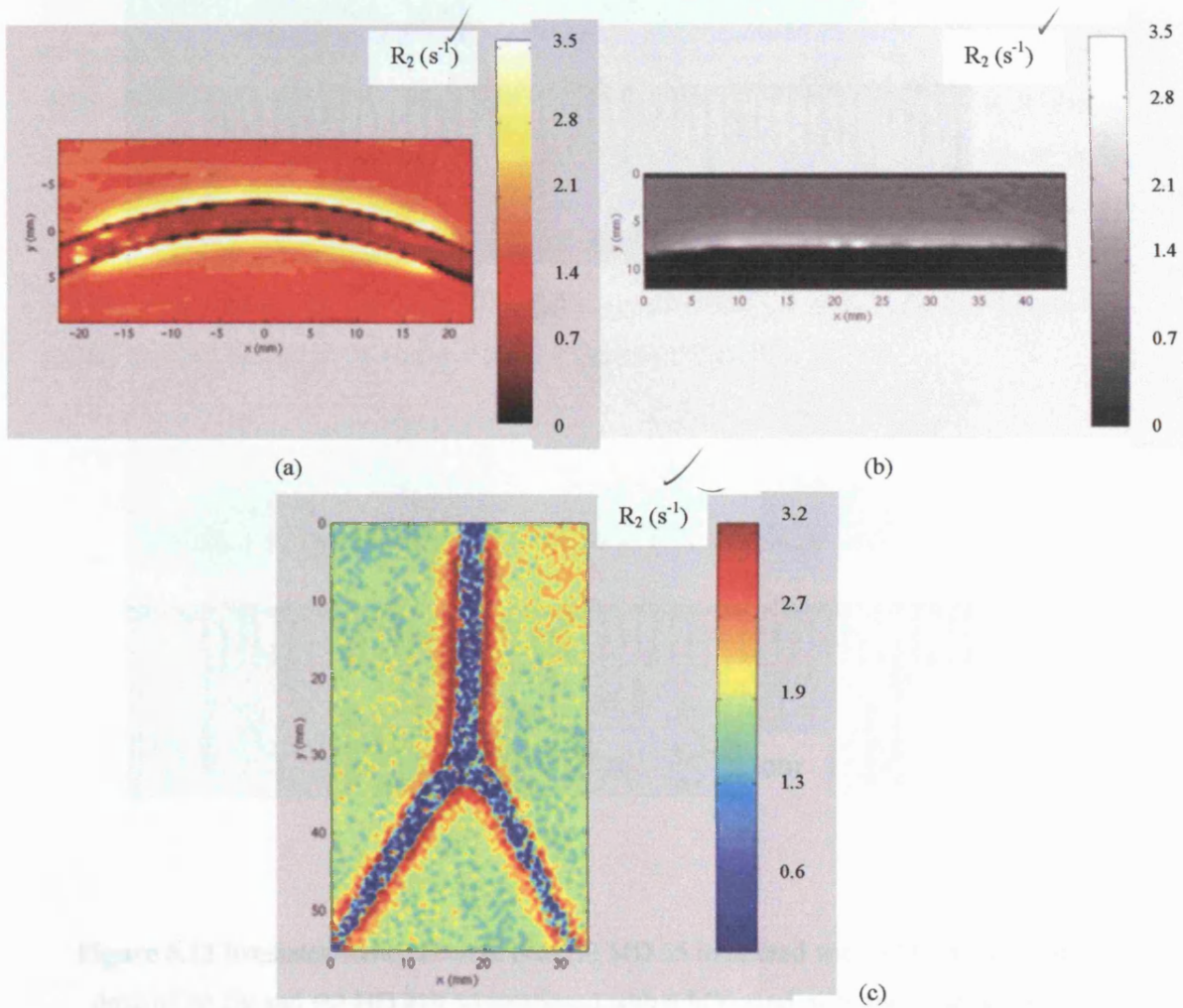
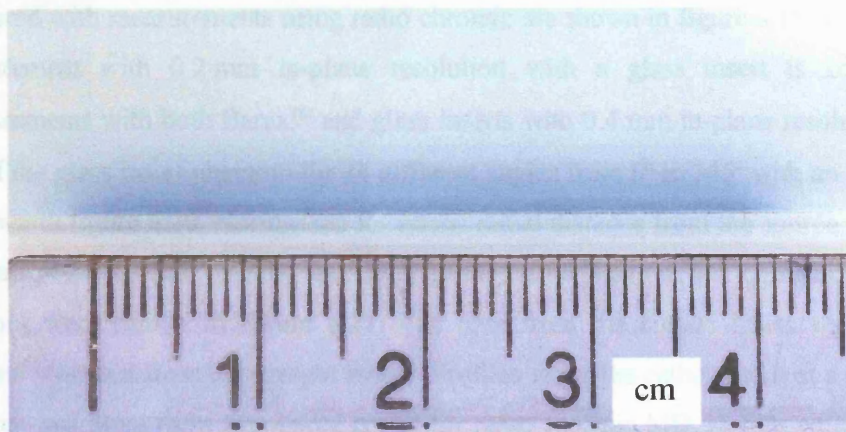
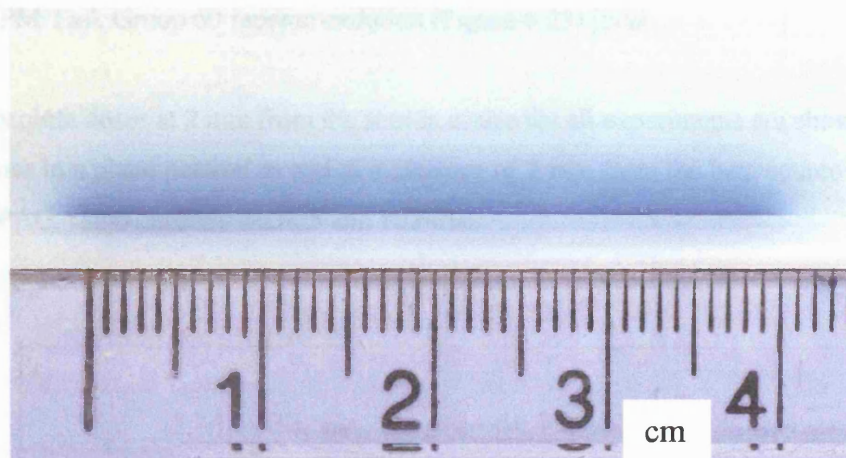


Figure 6.11 Longitudinal R_2 images of a PAG gel used as a (a) curved and (b) stent cardiovascular phantom with in-plane resolution of 0.4 mm and (c) bifurcation phantom with in plane resolution of 0.5 mm.

The results of the energy dependency of the radio chromic film are presented in figure 6.16a and 6.16b. The results showed no systematic variation with energy within the precision limit of the dosimeter over the range of electron and photon energies used. The densitometer evaluated the density to two decimal places and it may be possible that the densitometer was not sufficiently sensitive to detect small variations in response with energy.



(a)



(b)

Figure 6.12 Irradiated radio chromic film (a) MD 55 irradiated with 6 MV x-ray with the dose of 20 Gy and (b) HD 810 55 irradiated with 6 MV x-ray with the dose of 100 Gy.

The variation in absorbed dose with distance for both glass (0.2 mm in-plane resolution) and Barex™ inserts (0.25 mm in-plane resolution) together with the results obtained using radio chromic film are shown in figure 6.17. The achievable resolution was constrained by the

available scan time. There was no evidence of dose overestimation in the high dose area due to monomer diffusion during irradiation [De Deene et al 2001]. The irradiation times in this experiment were quite short compared to the long irradiation times (1024s) reported by De Deene et al. [2001]. The relative dose rates at radial distances from 2 to 6.2 mm for glass insert phantom in increments of 0.2 mm are also given in Table 6.2. Profiles along the catheter axis at a radial distance of 2 mm from the source centre for PAG with glass insert compared with measurements using radio chromic are shown in figure 6.18. In figure 6.19, a measurement with 0.2 mm in-plane resolution with a glass insert is compared with measurements with both Barex™ and glass inserts with 0.4 mm in-plane resolution. A radial plot of the glass insert phantom for 24 different angles from 0° to 345° with an interval of 15° is shown in figure 6.20. Normalised R_2 versus radial distance from the source centre at three different positions (left, middle and right) of the curve phantom and compared with straight phantom were shown in Figure 6.21. The data from the curved insert was found to be identical with that from the straight insert. Profiles along the catheter axis at a radial distance of 2 mm and 3mm from the source centre for radio chromic MD 55 film with metallic stent are shown in figure 6.22. All depth dose curves, profiles and radial plot are drawn according to AAPM Task Group 60 recommendation (Figure 6.23) [Nath et al 1999].

The absolute doses at 2 mm from the source centre for all experiments are shown in table 6.3. The dose in a plane parallel to and at a distance of 2 mm from the beta source was measured using PAG, radio chromic MD-55 and HD-810.

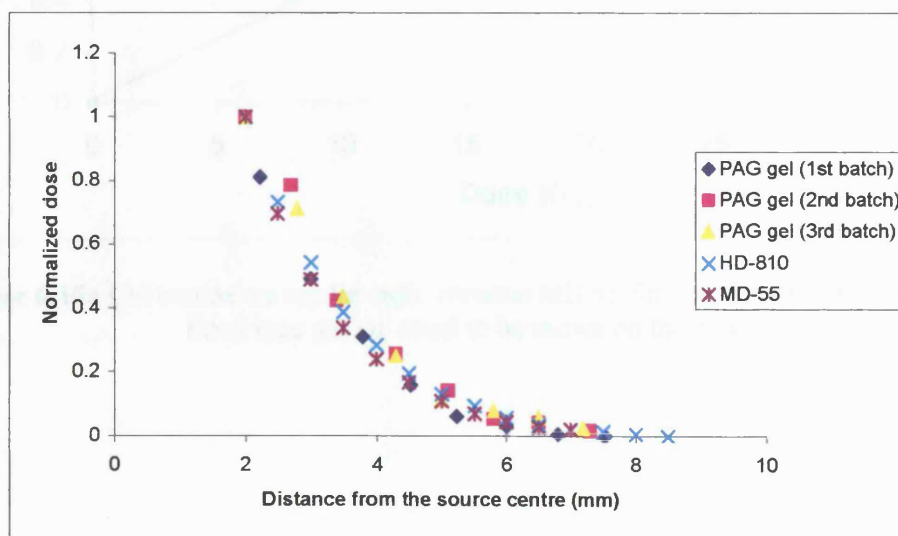


Figure 6.13 Relative dose normalized to 2 mm from the source centre and PAG gel data from 1 T MRI scanner.

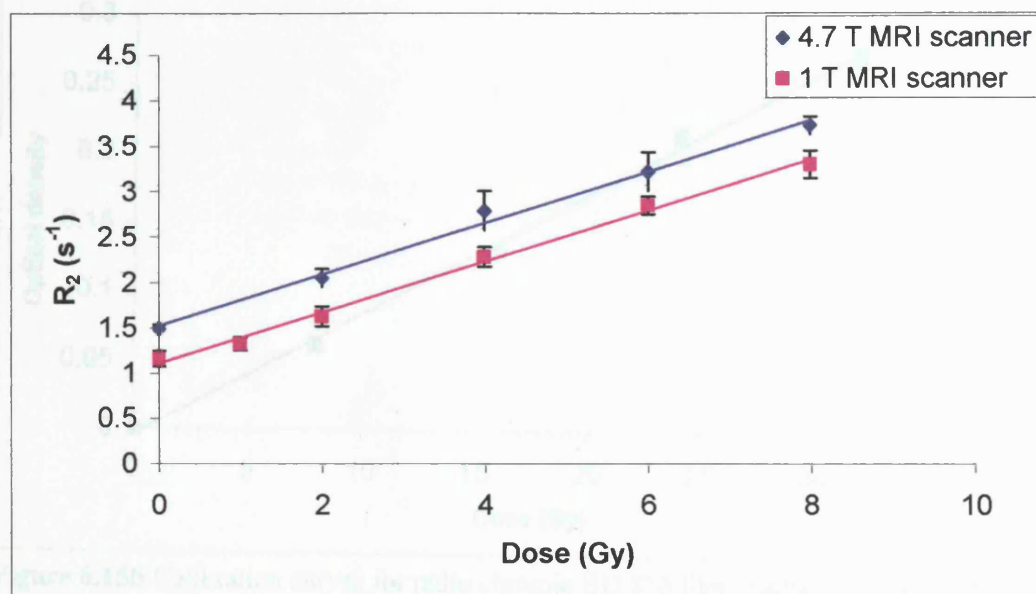


Figure 6.14 Calibration curves for a PAG measured using different MRI magnet strengths.

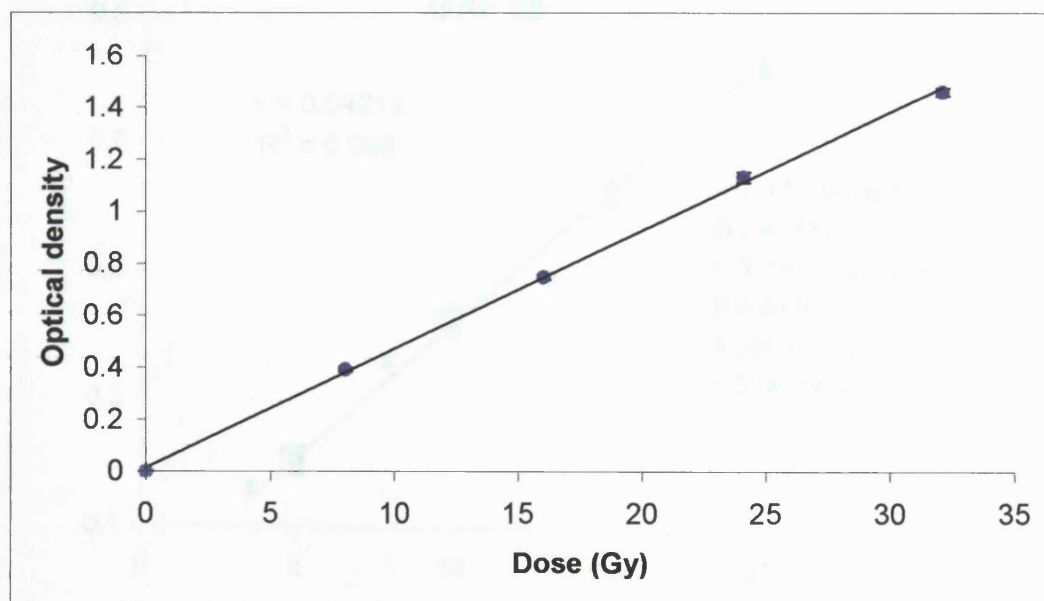


Figure 6.15a Calibration curves for radio chromic MD 55 film irradiated using 6 MV x-ray. Error bars are too small to be shown on this figure.

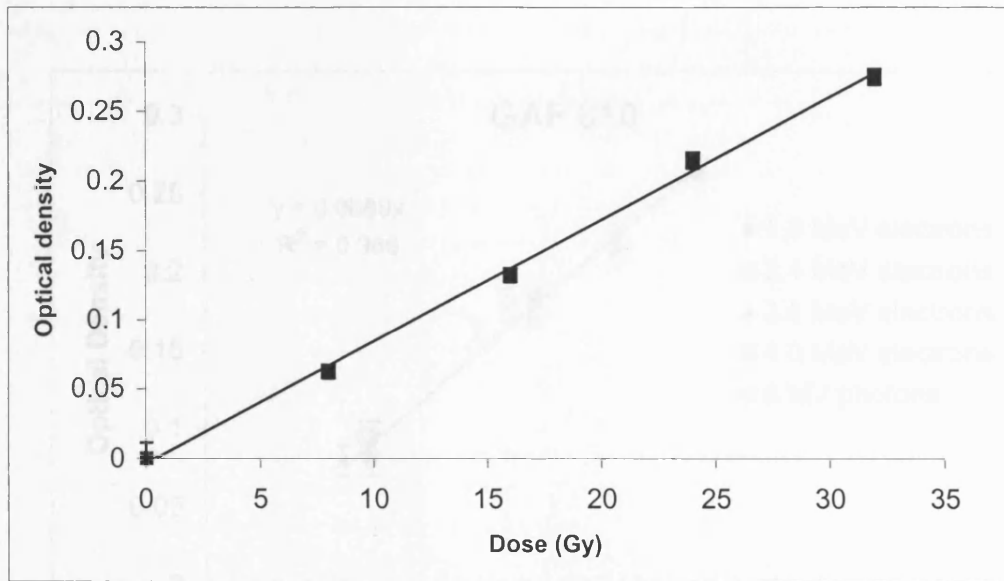


Figure 6.15b Calibration curves for radio chromic HD 810 film irradiated using 6 MV x-ray. Error bars are too small to be shown on this figure.

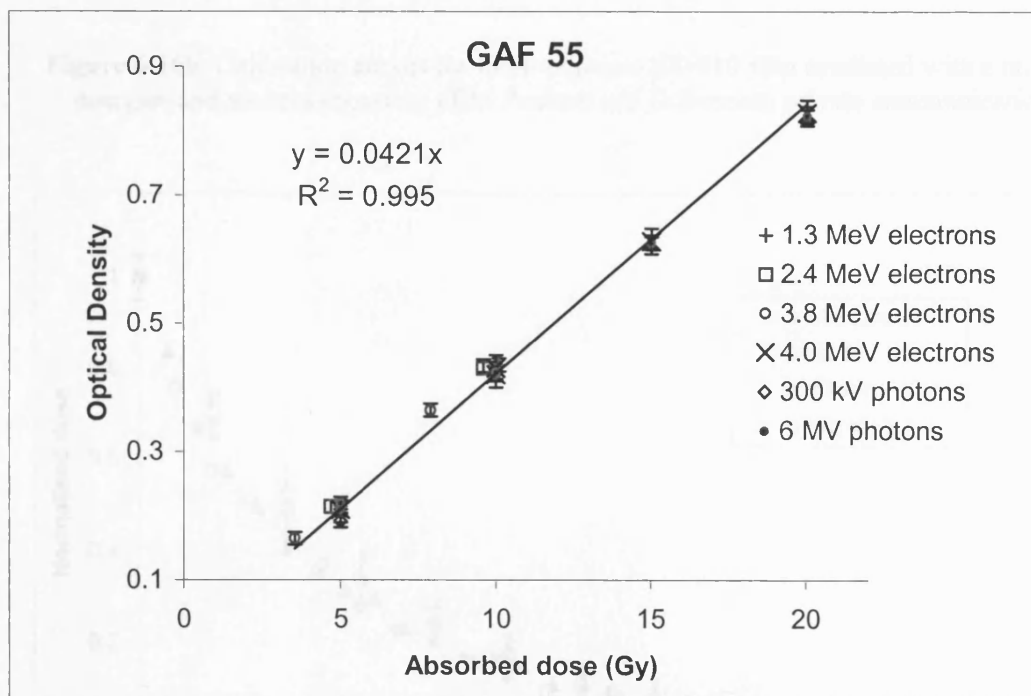


Figure 6.16a Calibration curves for radio-chromic MD 55 film irradiated with a range of energies and sources (courtesy of M Poulton and D Bonnett: private communication).

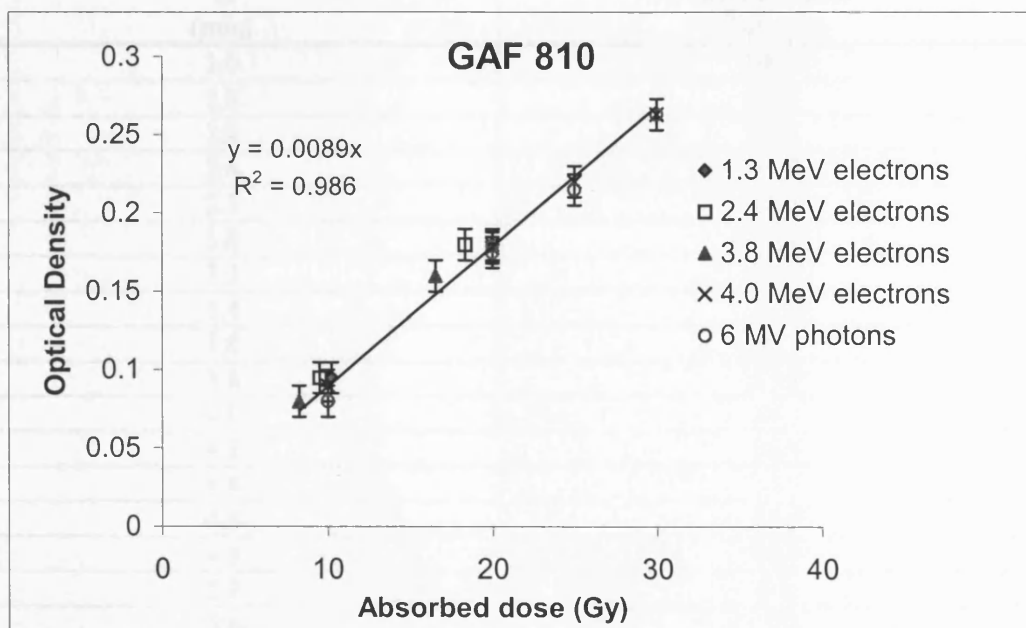


Figure 6.16b Calibration curves for radio-chromic HD 810 film irradiated with a range of energies and sources (courtesy of M Poulton and D Bonnett: private communication).

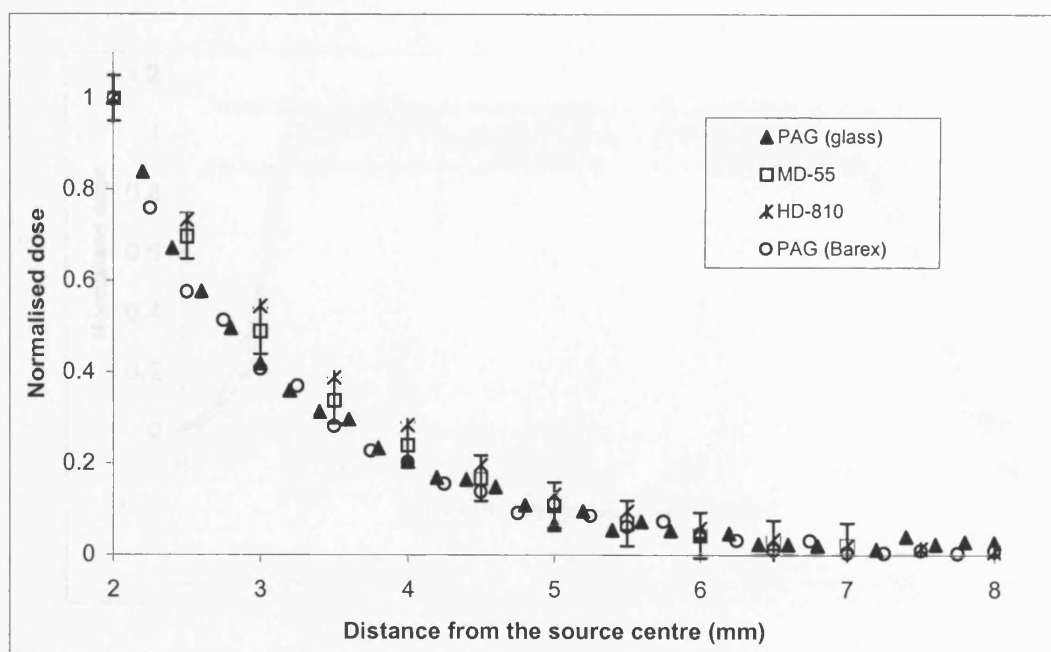


Figure 6.17 Relative absorbed dose measured orthogonally to the centre of the source train using PAG and radio chromic film. The results are normalized to 2 mm from the centre of the source train. The error bars for the gel data were omitted for the sake of clarity. Errors for the PAG data were estimated to be $\pm 6\%$ based on the variation in dose in the low dose region.

R (mm)	Relative dose Rate (%)
2.0	100.0
2.2	83.8
2.4	67.2
2.6	57.7
2.8	49.7
3.0	42.0
3.2	36.0
3.4	31.4
3.6	29.7
3.8	23.4
4.0	20.5
4.2	16.9
4.4	16.5
4.6	14.9
4.8	10.9
5.2	9.6
5.6	7.3
5.8	5.3
6.0	4.8
6.2	4.7

Table 6.2 Relative dose rate, normalized to 2 mm, as a function of radial distance from the centre of the catheter.

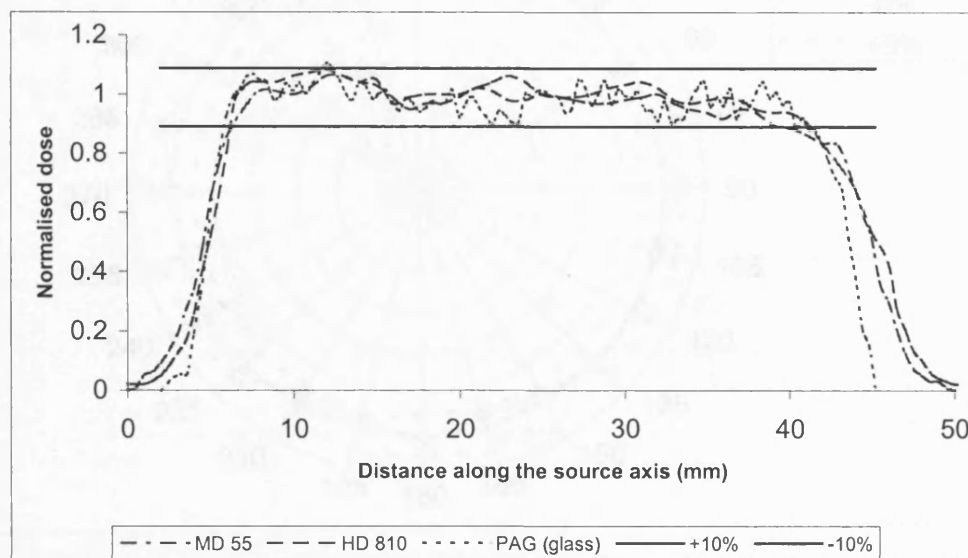


Figure 6.18 A comparison of profiles measured using PAG and GAF chromic film along the catheter axis at a radial distance of 2 mm from the source centre. For the sake of clarity, error bars are not shown. All data are normalised to the dose measured at distance along the source axis of 25 mm.

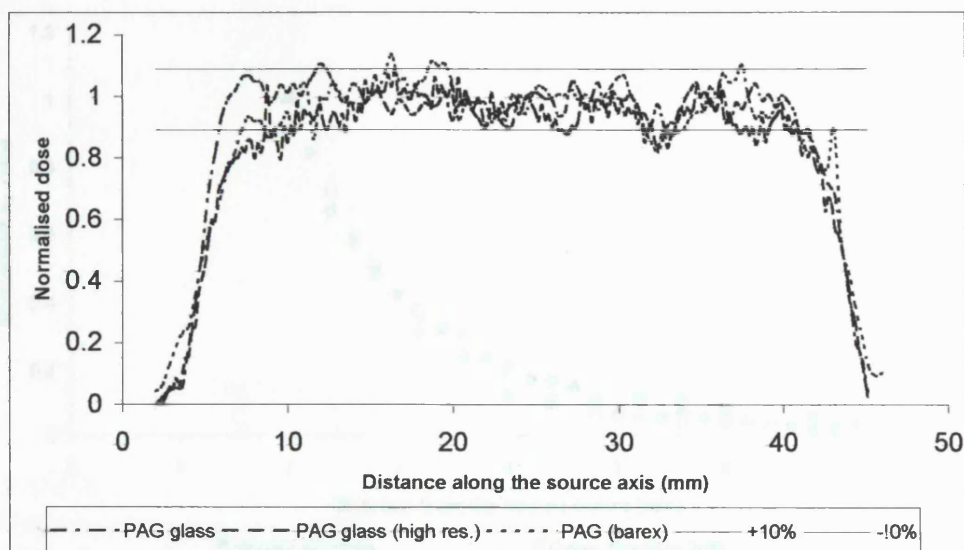


Figure 6.19 Measured profiles using PAG and imaged with in-plane resolutions of 0.4 mm compared with a glass insert imaged with 0.2 mm in-plane resolution. For the sake of clarity, error bars are not shown. All data are normalised to the dose measured at distance along the source axis of 25 mm.

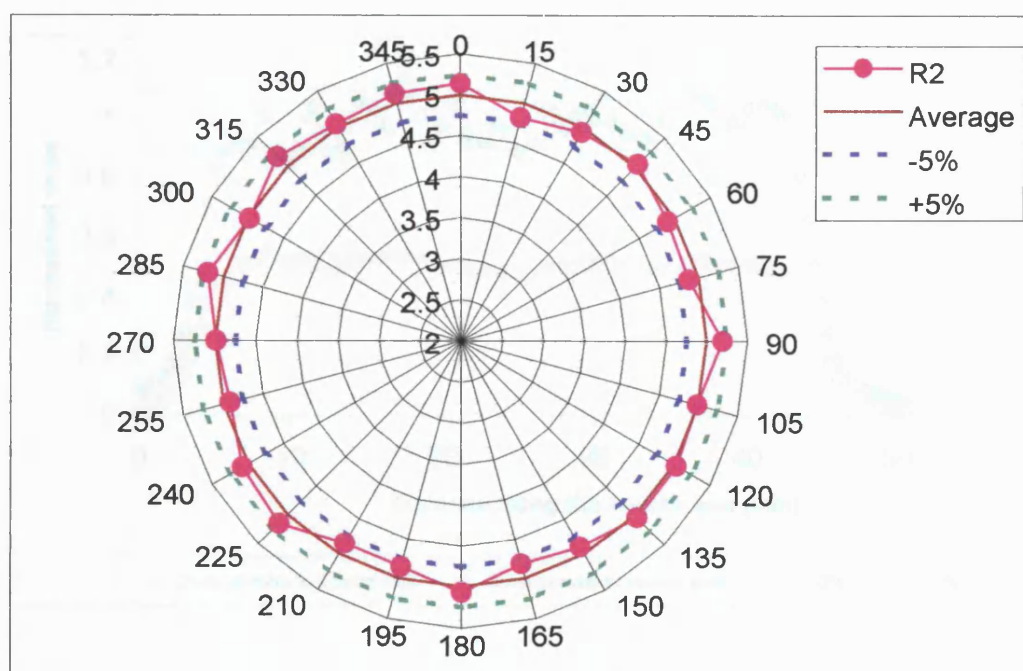


Figure 6.20 (Radial plot) radial uniformity of cardiovascular brachytherapy sources Sr-90. All data were measured at 2 mm radial distance from the source centre for 24 angles from 0° to 345° with an interval of 15°.

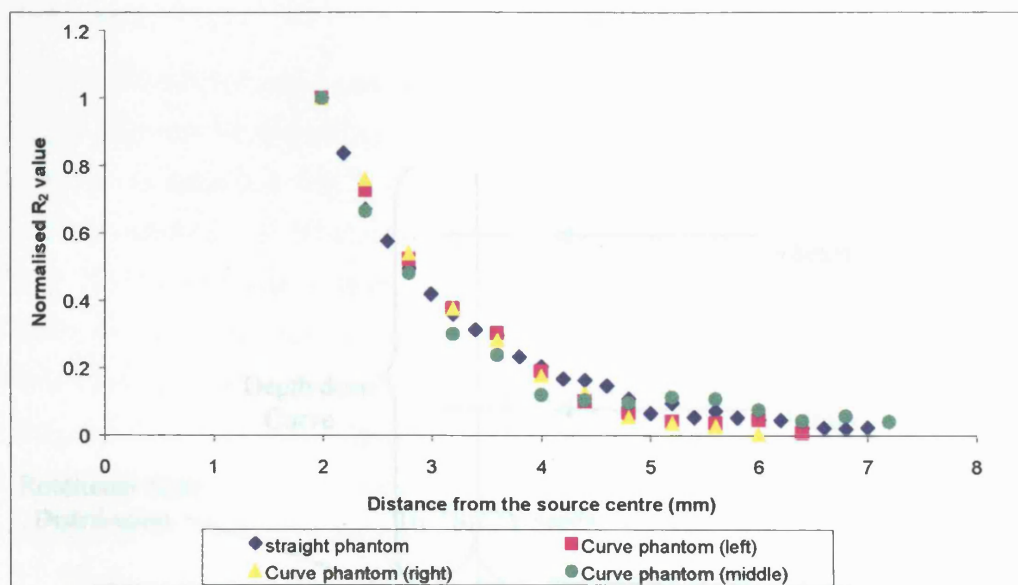


Figure 6.21 Measured depth dose curve at three different positions of the curved cardiovascular phantom and compared with the measured depth dose curve for the straight cardiovascular phantom.

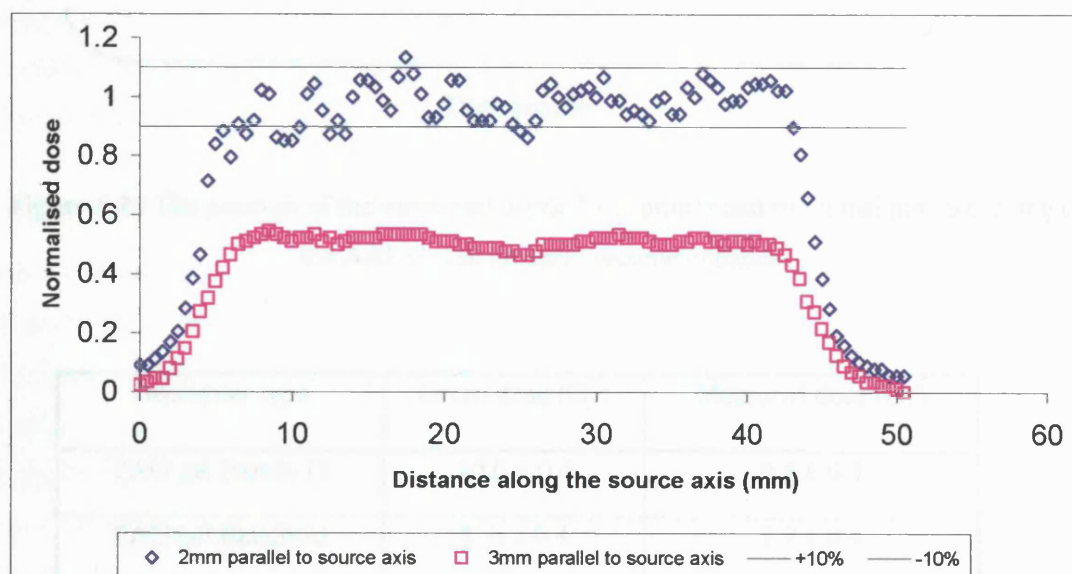


Figure 6.22 Measured profiles for radio chromic MD 55 film irradiated using $^{90}\text{Sr}/^{90}\text{Y}$ sources with a metallic (gold) stent. All data are normalised to the dose measured at distance along the source axis of 27.7 mm.

4. Discussion

For the PAG, the two calibration curves measured using MRI scanners with different strategies (figure 6.14) showed the same slope but different intercepts (change in the transverse relaxation rate). The results were considered to be largely independent of the magnetic field, and could be used at any field, which might explain some of the differences in the different magnetic field strength used for the measurements. In addition, the different magnetic field strength used for the measurements of the gradient through the PAG was also considered to be largely independent of the magnetic field.

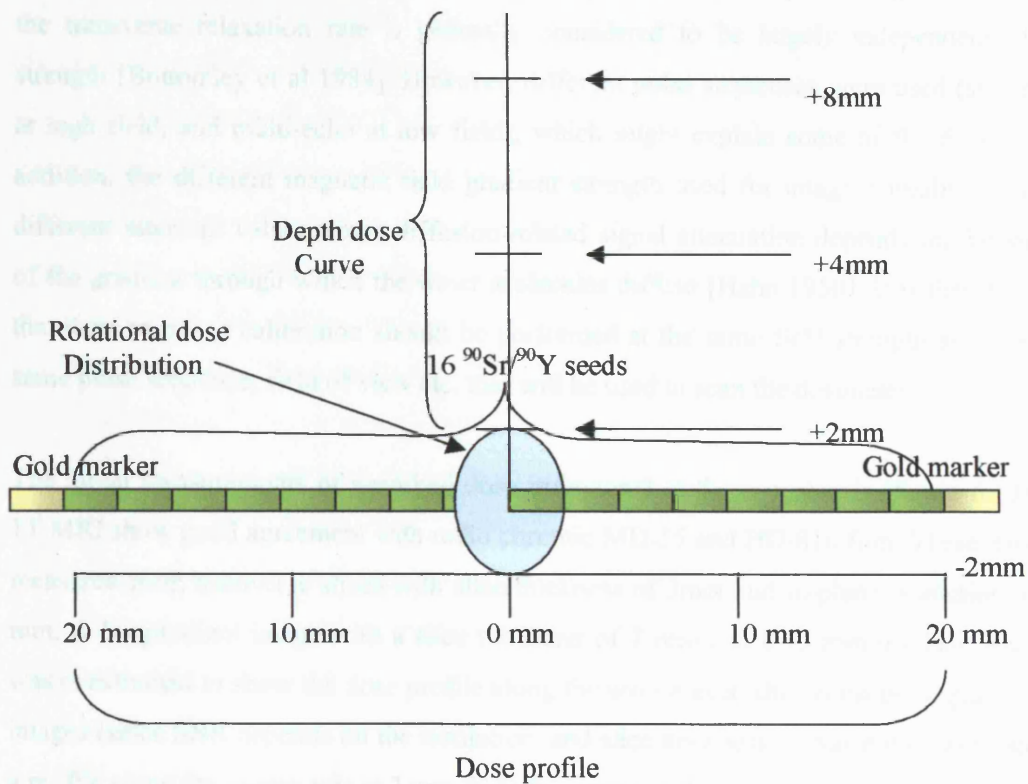


Figure 6.23 The position of the measured depth dose, profile and rotational plot according to the AAPM task group 60 recommendation.

Dosimeter type	Given dose (Gy)	Measured dose (Gy)
PAG gel (batch-1)	10.0 ± 0.4	9.4 ± 0.4
PAG gel (batch-2)	8.0 ± 0.4	7.9 ± 0.4
GAF chromic MD-55	20.0 ± 0.6	20.8 ± 0.9
GAF chromic HD-810	32.2 ± 0.9	32.4 ± 1.7

Table 6.3 Comparison of the absolute dose measured at 2 mm from the source centre.

4. Discussion

For the PAG, the two calibration curves measured using MRI scanners with different field strengths (figure 6.14) showed the same slope but different intercepts (background R_2), while the transverse relaxation rate is generally considered to be largely independent of field strength [Bottomley et al 1984]. However, different pulse sequences were used (single echo at high field, and multi-echo at low field), which might explain some of the difference. In addition, the different magnetic field gradient strength used for imaging might explain the different intercept values, since diffusion-related signal attenuation depends on the strength of the gradient through which the water molecules diffuse [Hahn 1950]. It is therefore clear that dose response calibration should be performed at the same field strength and using the same pulse sequence, field of view etc. that will be used to scan the dosimeter. ✓

The initial measurements of absorbed dose orthogonal to the source axis (figure 6.13) from 1T MRI show good agreement with radio chromic MD-55 and HD-810 film. These data were measured from transverse slices with slice thickness of 3mm and in-plane resolution of 0.75 mm. A longitudinal image with a slice thickness of 2 mm and 0.75 mm in-plane resolution was constructed to show the dose profile along the source axis. Due to the poor quality of the images (since SNR depends on the resolution, and slice thickness) it was not possible to draw a profile along the source axis at 2 mm from the centre of the sources.

The measurements of absorbed dose orthogonal to the source axis [figure 6.17] shows good agreement between the PAG and MD-55 radio chromic film. The HD-810 gives some slightly higher estimated doses. The thin glass-walled insert does not appear to make a significant difference compared with the tissue equivalent Barex™ insert. Normalised dose versus radial distance from the source centre at three different positions (left, middle and right) of the curve phantom were also plotted [figure 6.21] and compared with the depth dose curve of the cardiovascular glass phantom; no significant differences were observed except the fall off in dose at the end of the middle position. For depth dose curves, all data were normalised at 2 mm from the centre of the source. Radial R_2 distributions at 2 mm from the centre of the source at 24 different angles from 0° to 345° with an interval of 15° show all R_2 values lie within 5% [figure 6.20], which is well within the $\pm 10\%$ limit specified by AAPM TG 60 [Nath et al 1999].

For the profiles parallel to the source axis there is good agreement between the PAG with a glass insert (in-plane resolution 0.4 mm) and the two measurements with radio chromic film [figure 6.18] with the exception of the fall off in dose at the end of the train. Both film and PAG data were normalised to readings 12 mm from one end of the insert. Similar distributions were measured with the Barex insert [figure 6.19]. The profiles measured with the highest resolution (0.2 mm) with a glass insert [figure 6.19] show much more structure than the other measurements, with the exception of the measurements with the Barex™ insert [figure 6.19]. Undulations were also observed for all profiles although it might be expected that the dose would not be completely uniform along the source. There are several possible explanations for this. First is that the outer diameter of the source train was 0.64 mm while the inner diameter of the catheter was 0.81 mm, so it could be that the sources were slightly displaced from the catheter axis. Secondly, it is possible that the catheter was bent inside the hole of the phantom; however special care were taken that the catheter was kept straight, at least in the vicinity of the sources. Finally, there might have been small gaps between one seed and the next. Profiles at 2mm radial distance for MD 55 film with metallic stent [figure 6.22] shows more structure in comparison with the profile at 3 mm distance and also with the profile at 2 mm distance without stent insert [figure 6.18]. The metallic stent has a significant effect on dose distribution at least up to 2 mm radial distance in comparison with the profile at 3 mm distance, although the maximum and minimum variation lies within $\pm 10\%$. From the bifurcation phantom we could not get any useful information due to the poor quality of its construction, with 1mm thick glass.

The ability of PAG gels to measure absolute doses accurately has been the cause for much debate and large differences have been recorded [Farajollahi et al 1999, Low et al 1999, Cosgrove et al 2000]. It is possible that the size difference between the main phantom and calibration tubes is a contributory factor. Farajollahi *et al.* [2001] showed that the slope of the gel dose response was $0.24 \pm 0.01 \text{ s}^{-1} \text{ Gy}^{-1}$ for the calibration vials, and $0.33 \pm 0.003 \text{ s}^{-1} \text{ Gy}^{-1}$ for a large phantom. Another possible contributory factor is the temperature difference between the phantoms and calibration vials at the time of scanning, since R_2 is strongly dependent on the temperature. McJury *et al.* [1999b] have commented on this effect inside the RF coil. In addition, variations in the manufacturing process [Oldham et al 1998b] or of the thermal history of the samples [Salomons and Schreiner, 1999] may cause differences between calibration samples and phantoms. In this present set of experiments, calibration vials and phantoms have almost identical dimensions, so the effects of temperature and size difference will have been minimised. Furthermore, two batches of gel were made for this

study and gave similar results [table 6.3]. For the first batch, the dose along the source axis at 2 mm distance from the source centre was measured. The treated length was 40 mm and the given dose was 10 Gy at 2 mm from the source centre, while the measured dose was 9.4 ± 0.4 Gy. Uncertainty in the given dose was 1.6% (0.16 Gy for 10 Gy) according to the source calibration data. In addition, since there is a manual transport system, there are also timing errors. Estimated timing errors are of the order of 2 seconds, giving a further error in dose of ± 0.24 Gy at 2 mm radial distance. Thus, the total uncertainty for the errors summed in quadrature for a dose of 10 Gy was 0.4 Gy (4%). In the first experiment, the measured dose was 6.5% lower than the given dose. This was due to the fact that that it was not possible for the calibration vials and phantoms to be scanned on the same day. They were scanned several days apart but at the same temperature.

Within a region 33 mm along the source axis, the maximum dose recorded was 10.2 Gy, which is 8.6% higher than the mean dose, while the minimum dose recorded was 8.8 Gy, 6.2% lower than the mean. It should be mentioned here that for all experiments the absorbed doses were measured over the central two-thirds of the treated length. For the second measurement, the given dose at 2 mm from the source centre was 8.0 ± 0.4 Gy and the measured dose was 7.9 ± 0.4 Gy. The estimated dose is not significantly different from the given dose. In this case, both phantoms and calibration vials were measured on the same day. The maximum dose along this 36.4 mm distance recorded was 8.5 Gy, which is 6.8% higher than mean dose and the minimum dose recorded was 7.3 Gy, 7.5% lower than the mean. One possible cause of the difference between the maximum and minimum doses was the bending of the catheter within the tube, since the inner diameter of the tube is approximately 2 mm, while the outer diameter of the catheter is around 1.6 mm. Thus some of the sources may have been being slightly displaced from the catheter axis. In both experiments, the measured absorbed doses were slightly lower than the given dose, which could be because of extra absorption by the glass insert, which is denser than tissue. The Barex™ tube was neither uniformly circular, nor perfectly straight, so it was difficult to measure absolute dose accurately and this was not attempted.

For the MD-55 film, the dose was measured along a line parallel to the catheter axis, 33 mm in length, at a radial distance of 2 mm from the axis. In this experiment, the average estimated dose along the catheter axis was 20.8 ± 0.9 Gy and the given dose was 20 ± 0.6 Gy. Thus, the measured dose was only 4% higher than that prescribed. Along the treated length the highest recorded value was 22.5 Gy, which is 8.2% higher than the mean value,

and the lowest value was 18.8 Gy, 9.6% lower than the mean. The standard deviation was $\pm 4.2\%$ for the dose measured along the central 33 mm 2 mm from the catheter axis. For HD-810 similar results were obtained. The mean measured dose was 1.6% higher than the prescribed dose. Along the treated length the difference between the highest and lowest values and the mean value was 9.9% and 7.6% respectively. The standard deviation was $\pm 5.2\%$ for the dose measured 2 mm from the catheter axis. In all experiments the source train met all the AAPM Task Group 60 specifications and recommendations.

Chapter 7

Applications: High Energy Electrons and 300kV x-rays

7.1 Introduction

In radiotherapy, there are many clinical situations where the use of abutting photon and electron field is required, such as cranispinal irradiation, tangential breast and supraclavicular fields and the topic of this chapter, mixed photon and electron beams for the treatment of head and neck cancer. In the treatment of head and neck cancer a commonly employed boost strategy is to treat the anterior part of the tumor volume with opposed lateral fields of 4-6 MV photon beams, and to treat the posterior part with lateral electron beams with the energy range 9-12 MeV to protect the cord from an excessive radiation dose. Dose inhomogeneities (hot and cold spots) are observed at the field margins, which are clinically undesirable and which are due to the electron penumbra. The penumbra of the photon beam from a commercial linear accelerator is usually quite narrow, whereas the penumbra of an electron beam which is collimated by a cone or lead cut-out positioned close to the skin is also relatively sharp in the superficial layers but broadens rapidly with increasing depth due to lateral electron scatter. For one method of treatment, photon and electron fields are matched to the light beam edges without a gap [Dobbs et al 1999]. In this case there will be an overdose of up to 20 percent, but this is ignored because the overdosed volume is small, occurs in non-critical connective tissue, only applies for 20 to 25 percent of overall treatment, and does not cause any significant clinical effect [Dobbs et al 1999]. Another method of treatment, which may eliminate this problem, is to keep a small surface gap between the fields [Griffiths et al 1994]. The dosimetry of abutting photon and photon [Shackford et al 1996, Xing et al 1997], electron and electron [Kalend et al 1985, Kurup et al 1985, Ulnin et al 1996, Lachance et al 1997, McKenzie et al 1998] and electron and photon beams [Papiez et al 1992, Karlsson et al 1993, Johnson et al 1994, Sidhu et al 1995, Thesen et al 1995, Sun et al 1998, Li et al 1999] have been studied by several authors.

Papiez et al [1992] used penumbra spreading techniques, which reduced the effect of positioning errors on dose uniformity. A stepped edge attenuator was used to obtain a wider penumbra for the photon beam and a Lucite scatterer was used for the electron beam. It was concluded by the authors that the proposed technique for modifying the electron and

photon beam penumbra produces a relatively uniform dose distribution in the abutting region, which is comparatively insensitive to positioning errors. The same type of experiment was done by Li et al [1999]. In their experiment, the photon and electron fields were set up such that the photon field extended ~2 cm into the electron field in the abutting region and the overlapped photon beamed was broadened using a multileaf collimator. It was also shown by them that the dose uniformity was improved and the sensitivity of dose homogeneity to setup errors was reduced. Johnson et al [1994] studied the dosimetric effects of abutting 6 MV photon fields with 9 MeV electron fields at extended SSDs to assess changes in the 90% isodose width, dose uniformity in the target and the extent of hot and cold spots in the junction region. It was shown that a 20% hot spot occurred on the photon side because of the electron scatter from the adjoining field and the width of this hot spot increased dimensionally but not in magnitude as the electron SSDs were increased. It was also shown that the cold spot occurred on the electron side due to the decrease in the 90% isodose width at extended electron SSDs. This cold spot was minimal at shorter electron SSDs, but increased with increasing electron SSDs. The same type of experiment was carried out by Sidhu et al [1995]. In addition, they used a gap of 0.5 cm between the light field edges of the photon field and the electron field and showed that it reduced the hot spot from 20% to 10% on the side of photon field, but the cold spot on the side of the electron field increased to 20%. They recommended that no gap should be allowed between the photon fields and the extended SSD electron fields. Thesen et al [1995] investigated the optimal condition of field matching using 9MV photon and 8 to 10 MeV electron beams. The evaluation was performed using an automatic video-densitometer and digital image processing. They presented dose profiles at depths of 1.2 and 2.5 cm for straight unmodified beams. They also studied geometrical variations at the field margin, using a gap of 3mm or an overlap of 5 mm. This resulted in a local underdose of 75 to 80% or an overdose of 135 to 150% referring to the reference dose respectively, and this dose inhomogeneity occurred at a width of 1 cm around the field margins. They concluded that the matching of unmodified beams appeared to have an advantage compared to the matching of fields with broadened penumbras. Using film dosimetry, dose distributions were measured at depths of 1 cm and 3 cm in the junction of the abutting photon and electron fields for a hot-match set up by Sun et al [1998]. Two photon field setups laterally opposed and 5° shallow right and left anterior oblique fields were studied by them. Dose profiles were also measured by them using a 2mm overlap and a 2 mm gap between the

electron and photon fields to investigate the change in dose distributions due to setup uncertainties.

In the study presented in this chapter, the dosimetry across the junction between 6 MV photon and 12 MeV electron was investigated using both PAG gel and MAGIC gel [Fong et al 2001]. Three different setups of photon field have been studied: straight (gantry angle 0°) photon field, 5° (gantry angle 5°) and 10° (gantry angle 10°) angled to the electron field. Dose profiles at depths of 15 mm (dmax of 6 MV photon) and 25 mm (dmax of 12 MeV electron) in the abutting region have been plotted. Dose profiles at the same two depths across the junction for a 2 mm overlap and a 2 mm gap between two fields due to the setup uncertainties and also the deviation between the light field and the radiation field have also been measured. All of these results were compared using PAG gel and radiochromic film measurement.

7.2 Materials and Methods

PAG and MAGIC gel were prepared as described in section 4.4 and 5.2.1. The MRI pulse sequence for imaging the PAG gel employed an echo train length of 16, echo spacing 50 ms and initial TE of 50 ms, TR = 3000ms, a field-of-view (FOV) 192 mm and matrix size 256×256 for 0.75 mm in-plane resolution and a field-of-view (FOV) 300 mm and matrix size 192×256 for 1.17 mm in-plane resolution and slice thickness 3 to 10 mm.

For the MAGIC gel both multi-echo and single echo sequences were used. For the spin echo sequence a repetition time of 3000 ms was used with echo times of 25, 50, 75, and 100 ms. Field of view (FOV) was 192 for 0.75 mm in-plane resolution and 300 mm for 1.17 mm in-plane resolution and the matrix size was 192×256 . Slice thickness was 3 to 10 mm depending on the type of experiment, and transverse, sagittal and coronal images were generated. Acquisition time was 9 m 40 s for each echo time. For the multi-echo sequence an echo train length of 16 was used, with an initial echo time of 22.5 ms, and 22.5 ms increments. Repetition time was 3000 ms, field of view was 300 mm with the matrix size of 192×256 , slice thickness was 3-10 mm and in-plane resolution was 1.17mm.

7.3 Dosimetry across the junction of photon and electron fields

For this study, five Barex™ phantoms (200×120×50mm) were prepared for each gel (PAG and MAGIC) and irradiated with a single 12 MeV electron field and a 6MV photon field. The photon field was either parallel to the electron field, abutting, overlapping or at 2mm distance. In addition, the photon field was also angled at 5° or 10° to the electron field [figure 7.1]. Using the MAGIC gel, each phantom was irradiated using 12 MeV electrons with an absolute dose 10 of Gy at the depth of maximum dose with the field size of 10×10 cm and SSD (source to surface distance) of 95 cm and 6 MV x-rays with the same dose and same field size but the SSD was 100 cm. For the PAG gel, the absorbed dose for both electron and photon field was 4 Gy. The electron and photon energies and other parameters were the same as for the MAGIC gel. To give adequate backscatter, a 5 cm thick sheet of WT1 was placed behind the phantoms. Dose profiles were measured at depths of 15mm and 25mm.

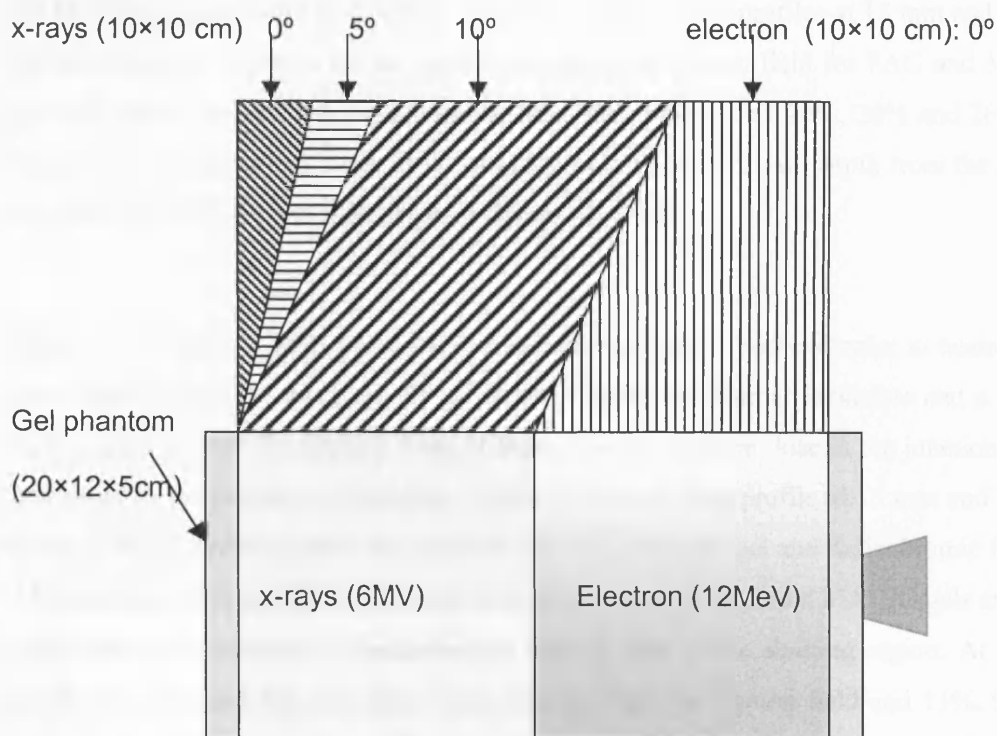


Figure 7.1 Experimental set up for irradiation with a single 12 MeV electron field and a 6 MV photon field. The phantoms were either parallel to the electron field or angled at 5° or 10° to the electron field.

The radio chromic film used in this study is known as MD-55 (Nuclear Associates). Details of the film and densitometer were given in section 6.2.4. A phantom was designed to irradiate the film using WT1 water equivalent plastic (St Bartholomew's Hospital London). The rectangular phantom was constructed in two halves with each being 30×30×5 cm in size and a 6×5 cm piece of film was carefully placed of the centre between the two halves of the phantom and the top of the film parallel to the top surface of the phantom. One half of the film was irradiated with 12 MeV electrons with the dose of 15 Gy and other half was irradiated with 6 MV x-rays with the dose of 15 Gy. To get the sufficient backscatter a 5 cm thick sheet of WT1 was also placed behind the phantom. Five pieces of film were irradiated in the same fashion as the gel.

Figure 7.2 shows the plane parallel to beam image and plane perpendicular to beam image (at 25 mm depth) for the PAG gel with parallel electron and photon fields. It shows a higher dose at the edge of photon field, which increases with the increasing depth due to the broadening penumbra of electrons. Figure 7.3 shows dose profiles at 15 mm and 25 mm depths across the junction for the parallel electron and photon field for PAG and MAGIC gel and compares then with radiochromic film. The result shows 20%, 20% and 26% over dose at 15 mm depth and 19%, 28%, and 26% over dose at 25 mm depth from the surface for PAG, MAGIC gel and radiochromic film respectively.

Figure 7.4 shows the MRI plane parallel to beam and plane perpendicular to beam (at 25 mm depth) images of PAG gel for an electron field with normal incidence and a photon field angled at 5° to the electron field. It shows a more uniform dose in the junction region compared to the previous experiment. Figure 7.5 shows dose profile at 15 mm and 25 mm depth from the surface across the junction for PAG, MAGIC gel and radiochromic film. At 15 mm depth, 10% and 8% under dose was recorded using PAG and MAGIC gels and 12% under dose was recorded by radiochromic MD 55 film in the abutting region. At 25 mm depth 7%, 13% and 5% over dose were recorded near the photon field and 11%, 9% and 10% under dose were recorded near the electron field for PAG, MAGIC gel and radiochromic film respectively.

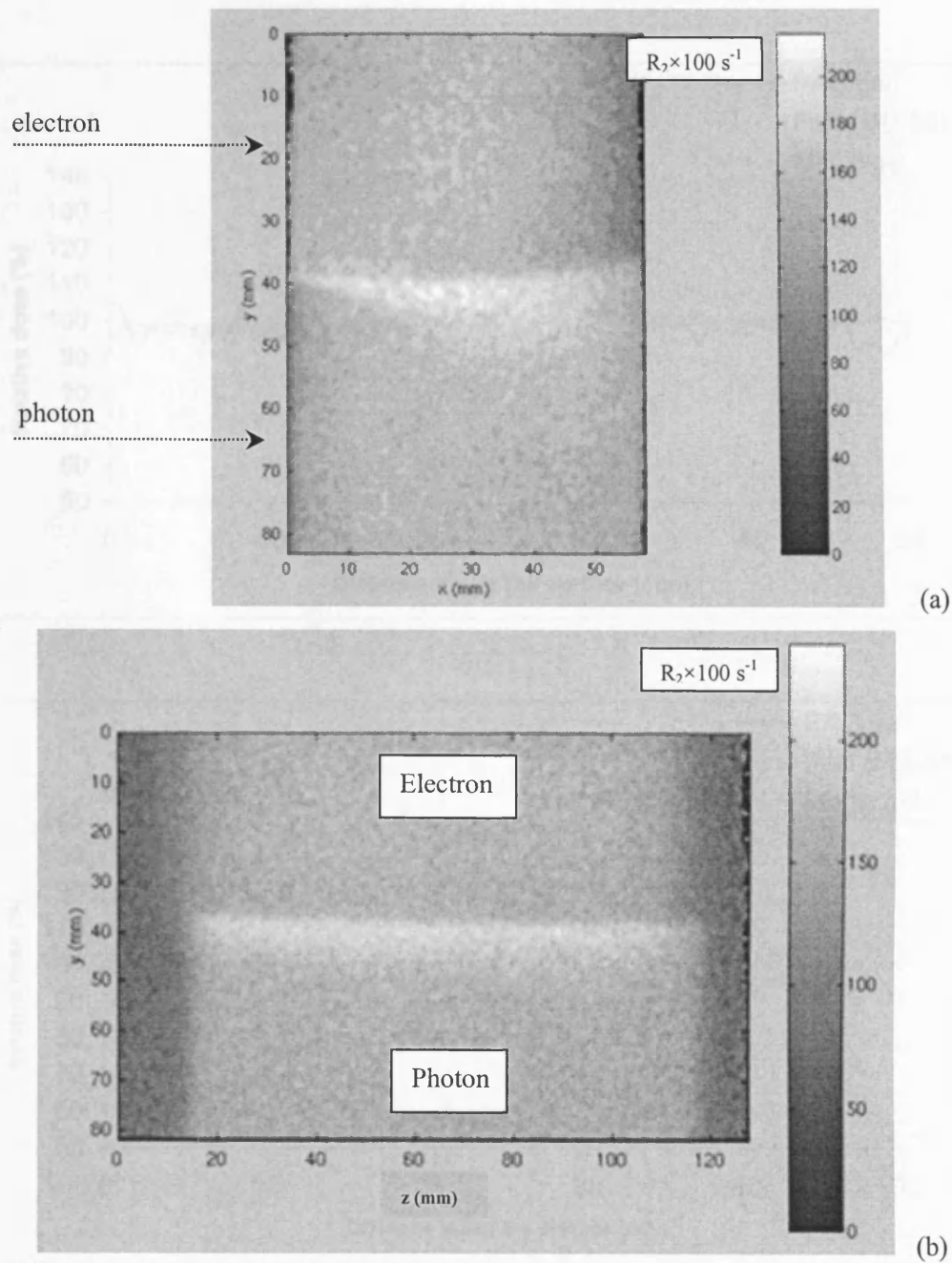
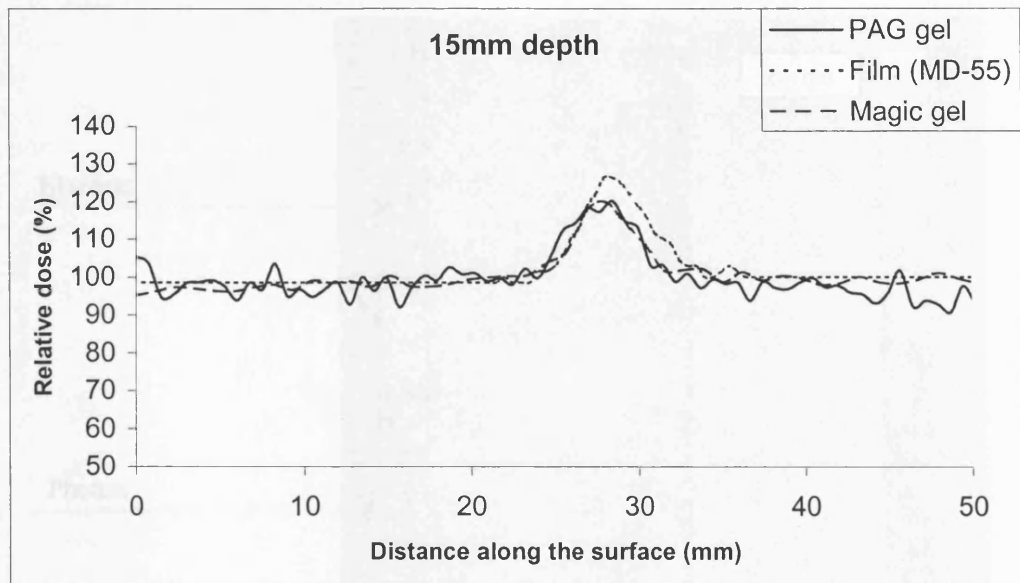
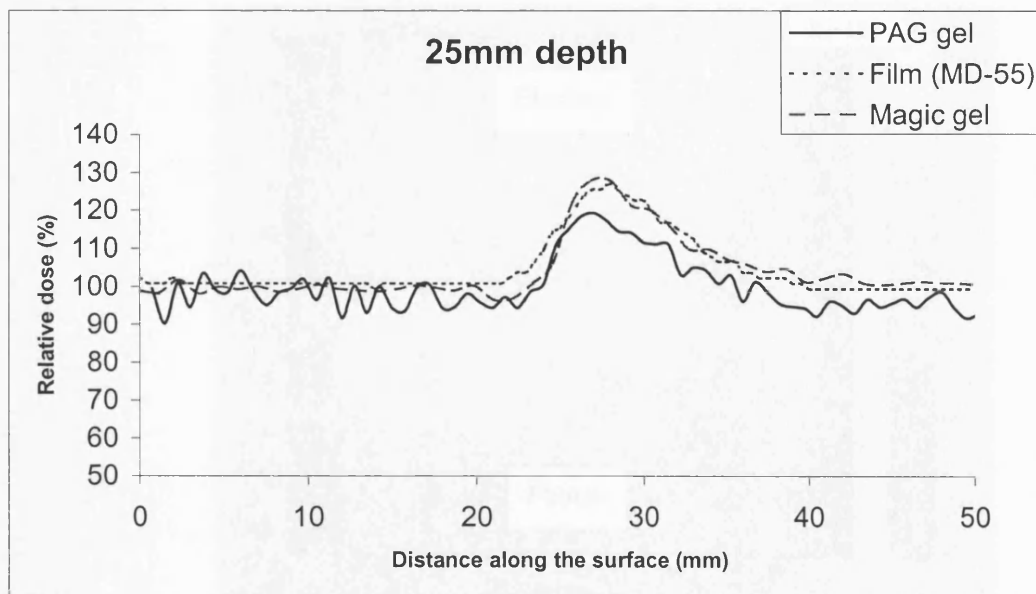


Figure 7.2 MR images of the PAG type gels (a) plane parallel to beam and (b) plane perpendicular to beam (2.5 cm depth) obtained from abutting a 6 MV, $10 \times 10 \text{ cm}^2$, 100 cm SSD photon field (gantry angle 0°) with a 12 MeV, $10 \times 10 \text{ cm}^2$, 95 cm SSD electron field (gantry angle 0°).



(a)



(b)

Figure 7.3 Profiles at (a) 15 mm and (b) 25 mm depth from the surface, where the gantry angle for both x-rays and electrons was 0°.

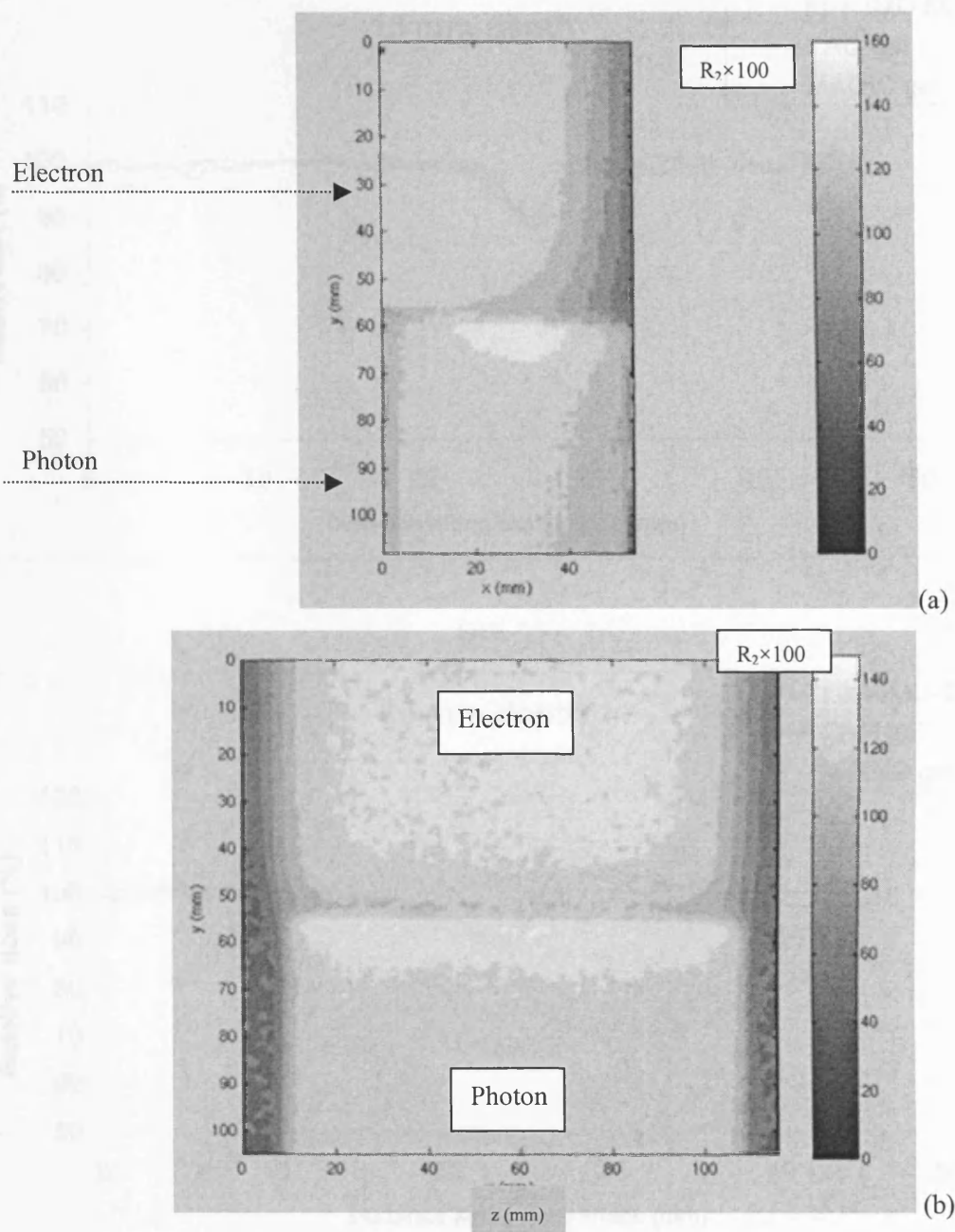
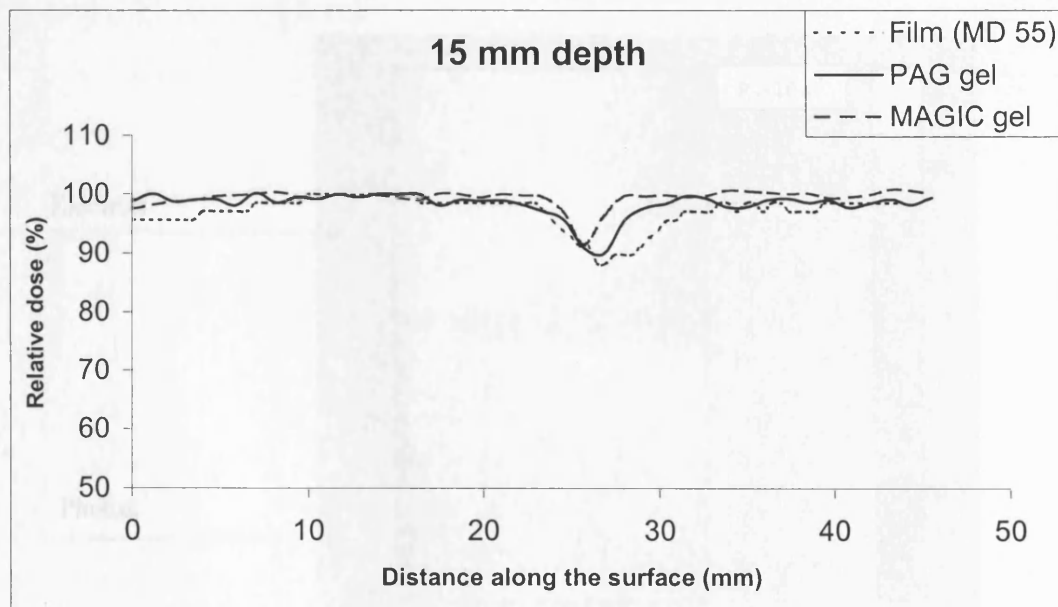
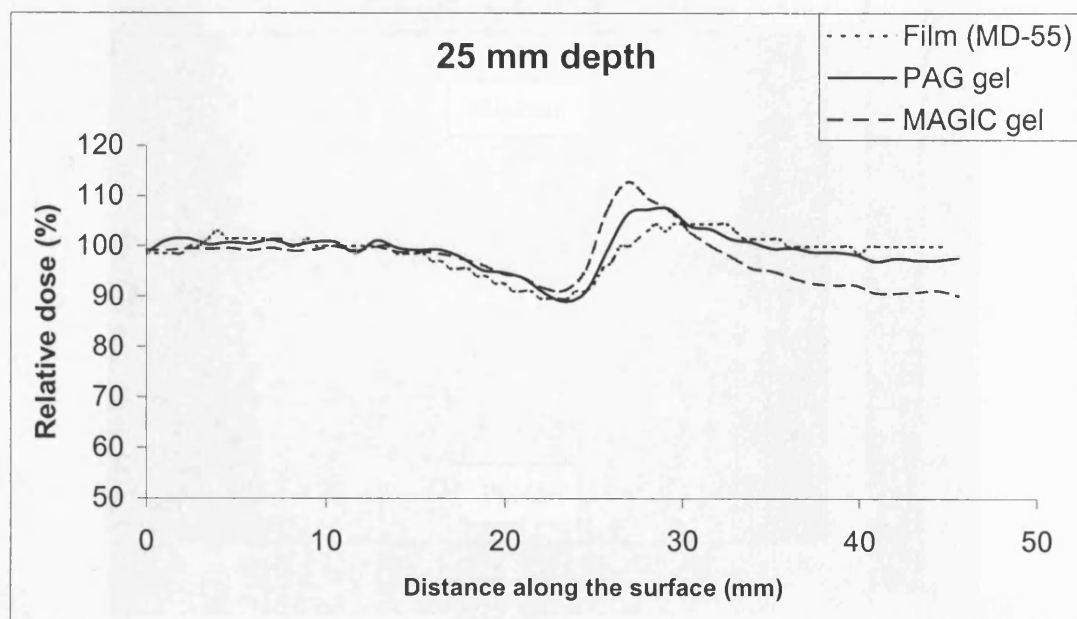


Figure 7.4 MR images (PAG) (a) plane parallel to beam and (b) plane perpendicular to beam at 2.5 cm depth from the surface obtained from abutting a 6 MV, $10 \times 10 \text{ cm}^2$, 100 cm SSD photon field (gantry angle 5°) with a 12 MeV, $10 \times 10 \text{ cm}^2$, 95 cm SSD electron field (gantry angle 0°).



(a)



(b)

Figure 7.5 Profiles at (a) 15 mm and (b) 25 mm depth from the surface, where the gantry angle for x-rays was 5° and for electrons was 0°.

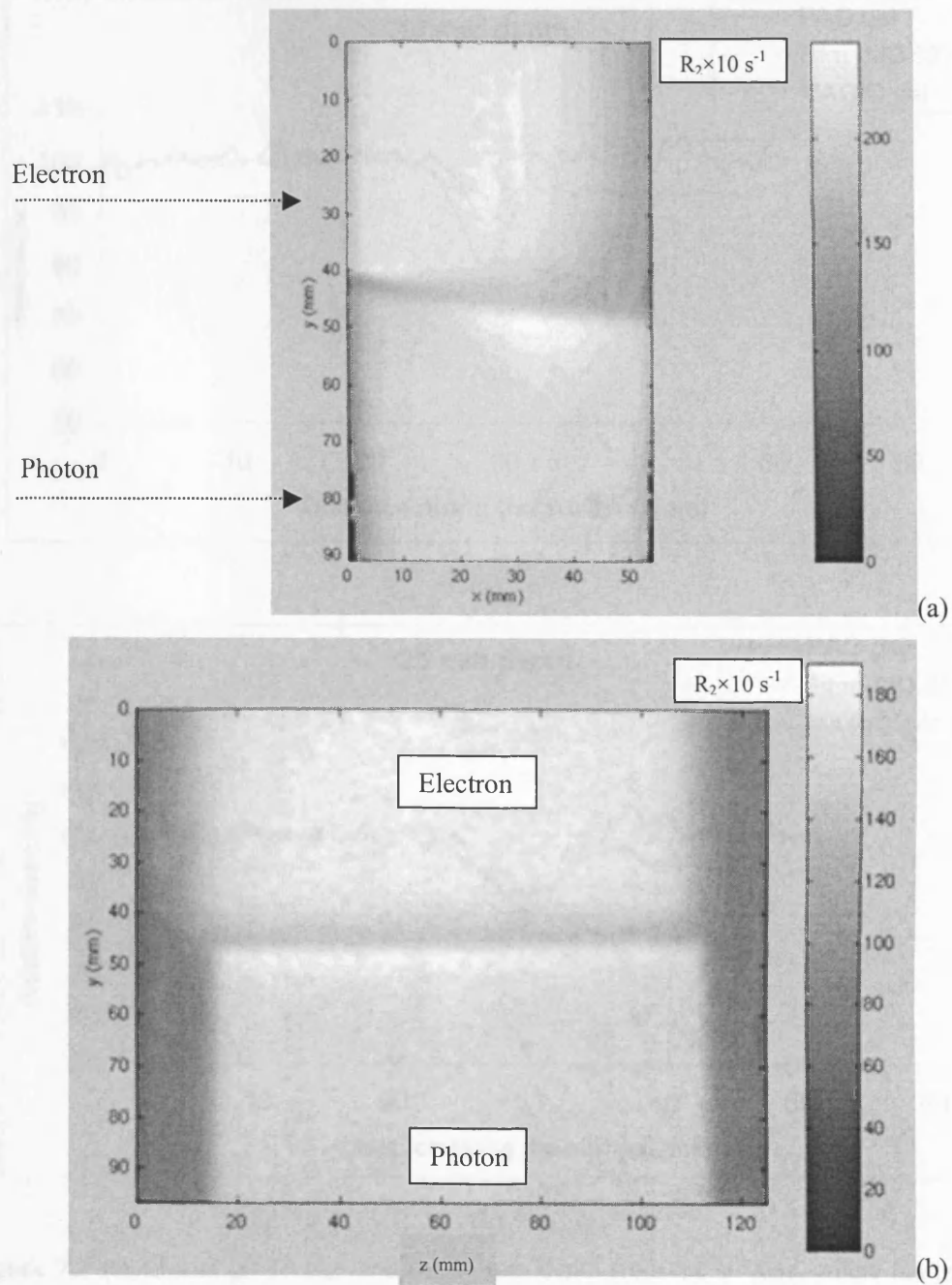
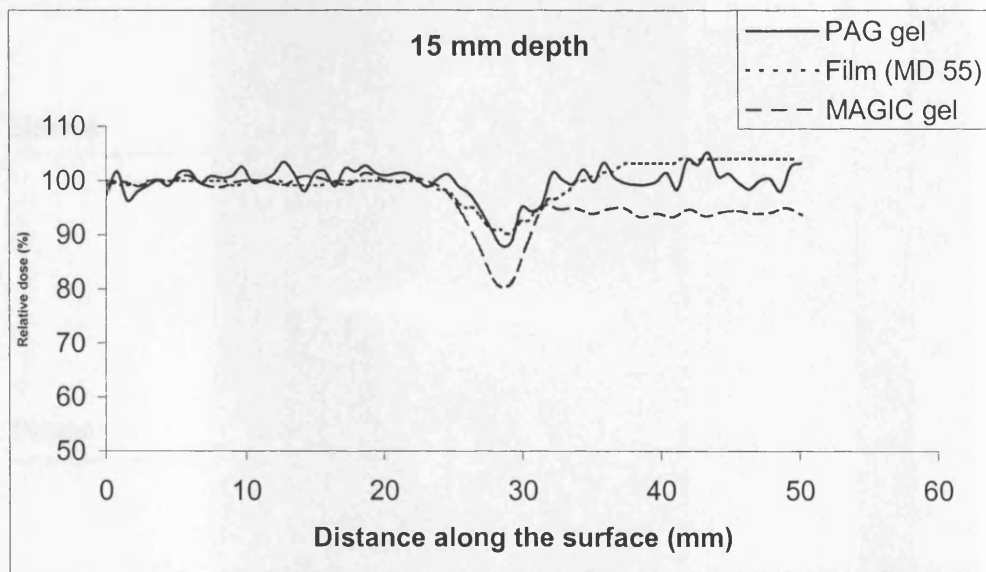
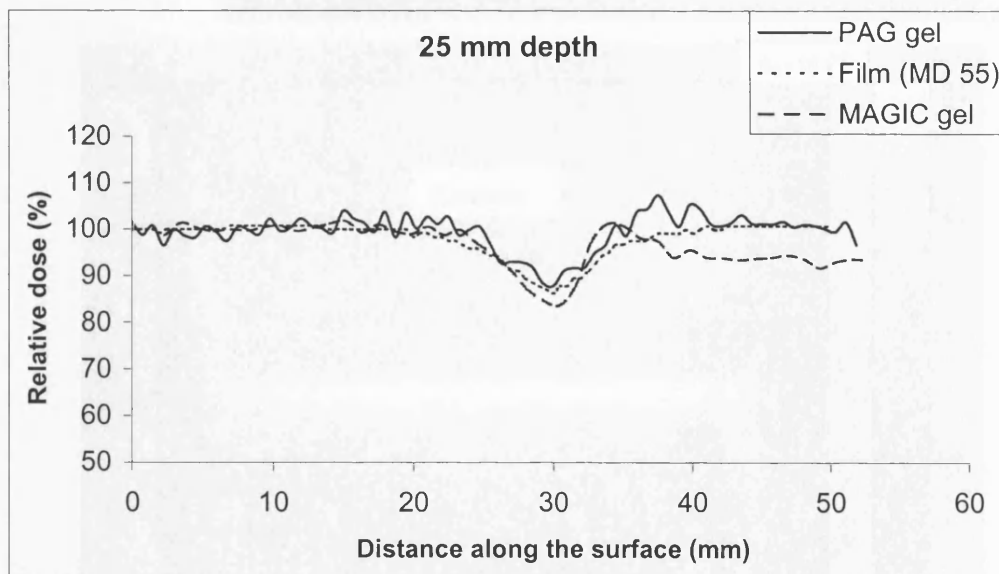


Figure 7.6 MR images (MAGIC) (a) plane parallel to beam and (b) plane perpendicular to beam at 2.5 cm depth from the surface obtained from abutting a 6 MV, $10 \times 10 \text{ cm}^2$, 100 cm SSD photon field (gantry angle 10°) with a 12 MeV, $10 \times 10 \text{ cm}^2$, 95 cm SSD electron field (gantry angle 0°).



(a)



(b)

Figure 7.7 Profiles at (a) 15 mm and (b) 25 mm depth from the surface, where the gantry angle for x-rays was 10° and for electrons was 0° .

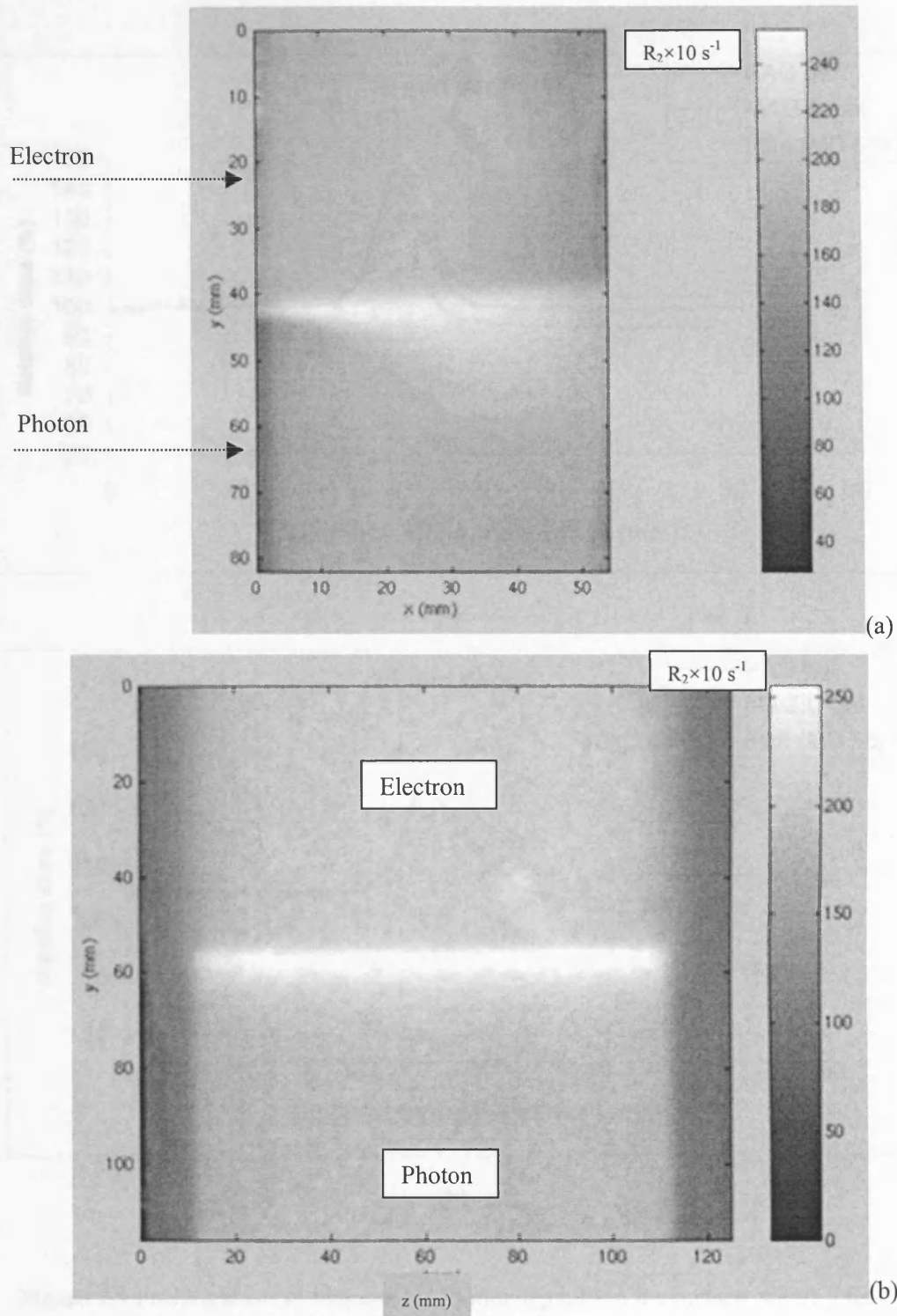
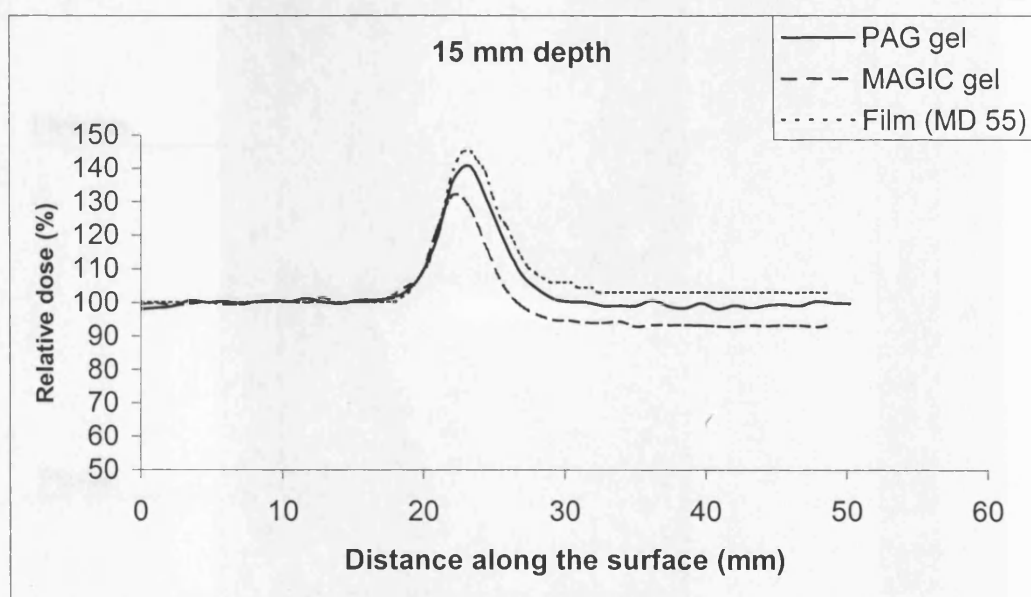
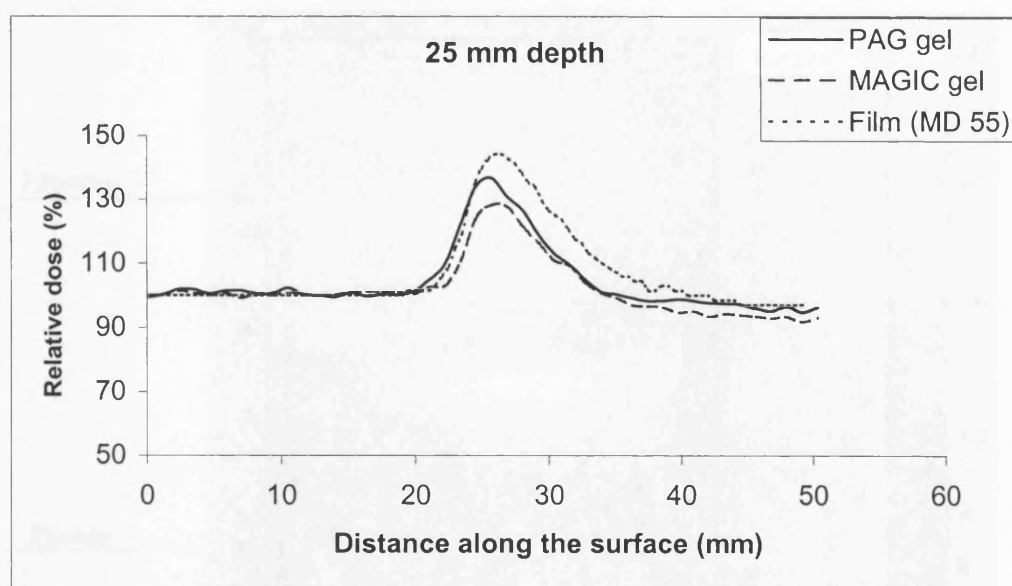


Figure 7.8 MR images of the MAGIC gel (a) plane parallel to beam (b) plane perpendicular to beam (at 2.5cm depth) for 2 mm overlap of a 6 MV, $10 \times 10 \text{ cm}^2$, 100 cm SSD photon field with a 12 MeV, $10 \times 10 \text{ cm}^2$, 95 cm SSD electron field.



(a)



(b)

Figure 7.9 Profiles at (a) 15 mm and (b) 25 mm depth from the surface, where 2 mm overlap of a 6 MV, $10 \times 10 \text{ cm}^2$, 100 cm SSD photon field with a 12 MeV, $10 \times 10 \text{ cm}^2$, 95 cm SSD electron field.

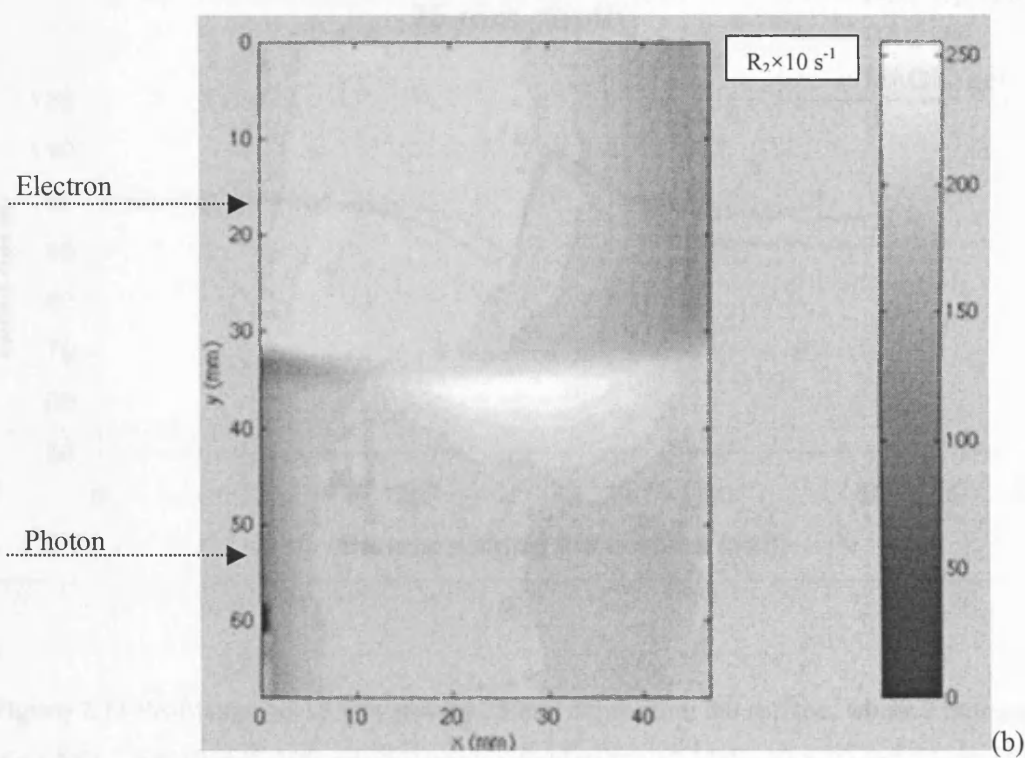
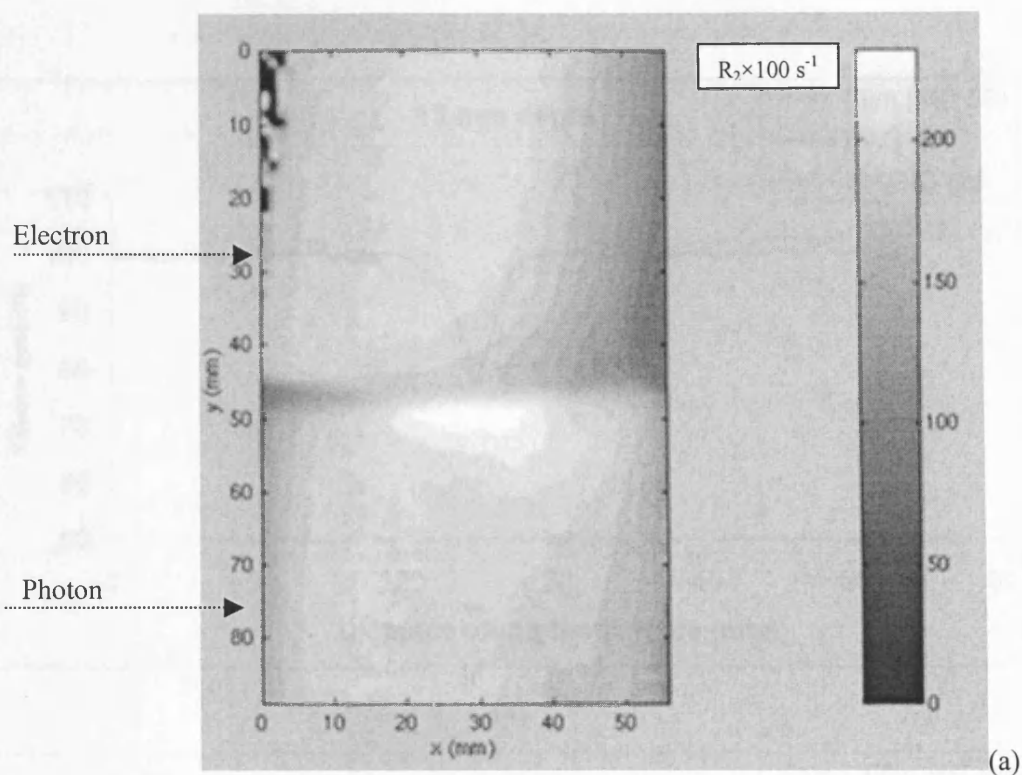
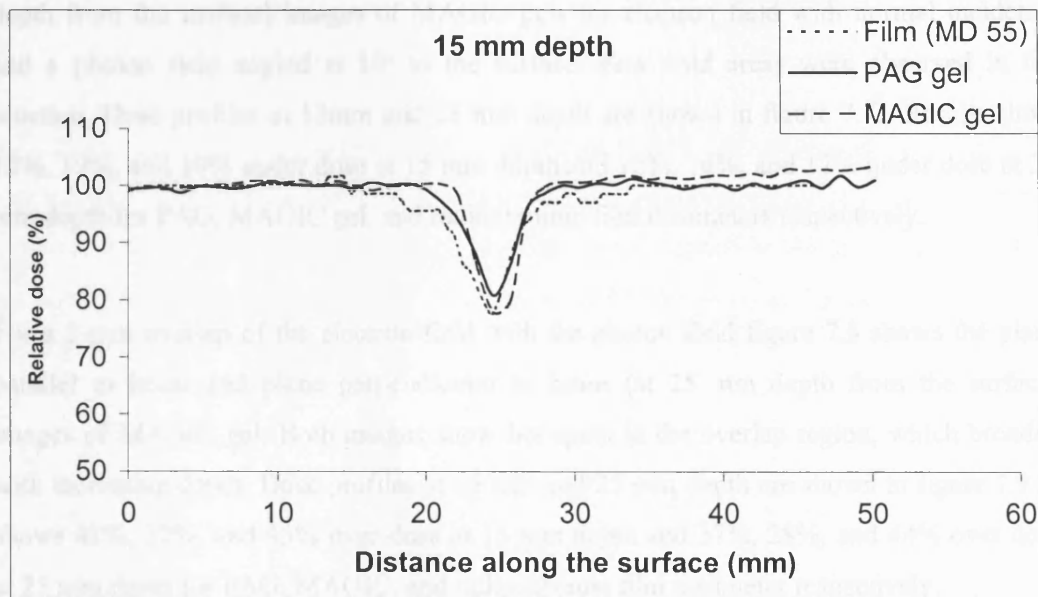
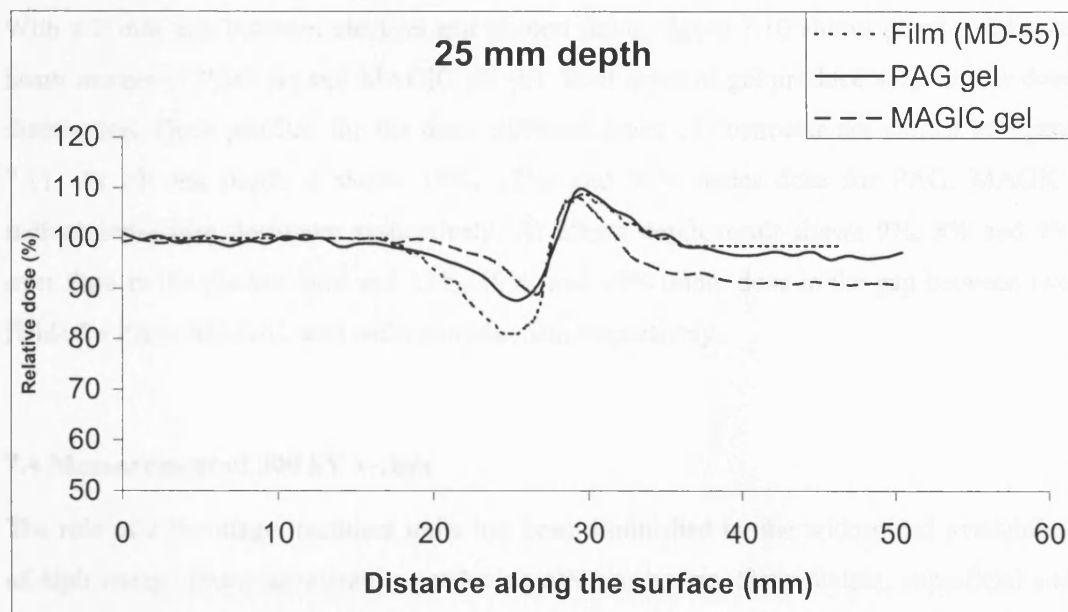


Figure 7.10 MR images (a) PAG (b) MAGIC plane parallel to beam for 2 mm gap of a 6 MV, $10 \times 10 \text{ cm}^2$, 100 cm SSD photon field with a 12 MeV, $10 \times 10 \text{ cm}^2$, 95 cm SSD electron field.



(a)



(b)

Figure 7.11 Profiles at (a) 15 mm and (b) 25 mm depth from the surface, where 2 mm gap of a 6 MV, $10 \times 10 \text{ cm}^2$, 100 cm SSD photon field with a 12 MeV, $10 \times 10 \text{ cm}^2$, 95 cm SSD electron field.

Figure 7.6 shows the plane parallel to beam and plane perpendicular to beam (at 25 mm depth from the surface) images of MAGIC gels for electron field with normal incidence and a photon field angled at 10° to the surface. Few cold areas were observed in the junction. Dose profiles at 15mm and 25 mm depth are shown in figure 7.7. Results show 12%, 19%, and 10% under dose at 15 mm depth and 12%, 16%, and 12% under dose at 25 mm depth for PAG, MAGIC gel, and radiochromic film dosimeters respectively.

For a 2 mm overlap of the electron field with the photon field figure 7.8 shows the plane parallel to beam and plane perpendicular to beam (at 25 mm depth from the surface) images of MAGIC gel. Both images show hot spots in the overlap region, which broaden with increasing depth. Dose profiles at 15 mm and 25 mm depth are shown in figure 7.9. It shows 41%, 32%, and 45% over dose at 15 mm depth and 37%, 28%, and 44% over dose at 25 mm depth for PAG, MAGIC, and radiochromic film dosimeter respectively.

With a 2 mm gap between electron and photon fields, figure 7.10 shows plane parallel to beam images of PAG (a) and MAGIC gel (b). Both types of gel produce very similar dose distribution. Dose profiles for the three different types of dosimeter are shown in figure 7.11. At 15 mm depth it shows 19%, 22%, and 21% under dose for PAG, MAGIC, radiochromic film dosimeter respectively. At 25mm depth result shows 9%, 8% and 9% over dose in the photon field and 12%, 10%, and 19% under dose in the gap between two fields for PAG, MAGIC, and radio chromic film respectively.

7.4 Measurement of 300 kV x-rays

The role of kilovoltage treatment units has been diminished by the widespread availability of high energy linear accelerators producing electron beams. Nevertheless, superficial and orthovoltage machines remain an essential part of many departments. They are still used for lesions near the skin surface, which are too deep for adequate treatment using x-rays in the range 50-150kV.

The purpose of this study was to measure depth dose curves using PAG and MAGIC gel with and without an ionisation chamber insert and to compare the results with BJR

supplement 17 [1983] and to investigate how the ionisation chamber perturbs the radiation field.

Two rectangular shaped phantoms were constructed with the dimension of $19.5 \times 12.5 \times 5.2$ mm using 1 mm thick Barex™ sheet. One of them included an insert for an ionisation chamber holder. The ionization chamber holder was inserted at 42 mm from the front surface of the phantom [figure 7.12]. The dimensions of the ion chamber region were 7 mm outer diameter and 25 mm length.

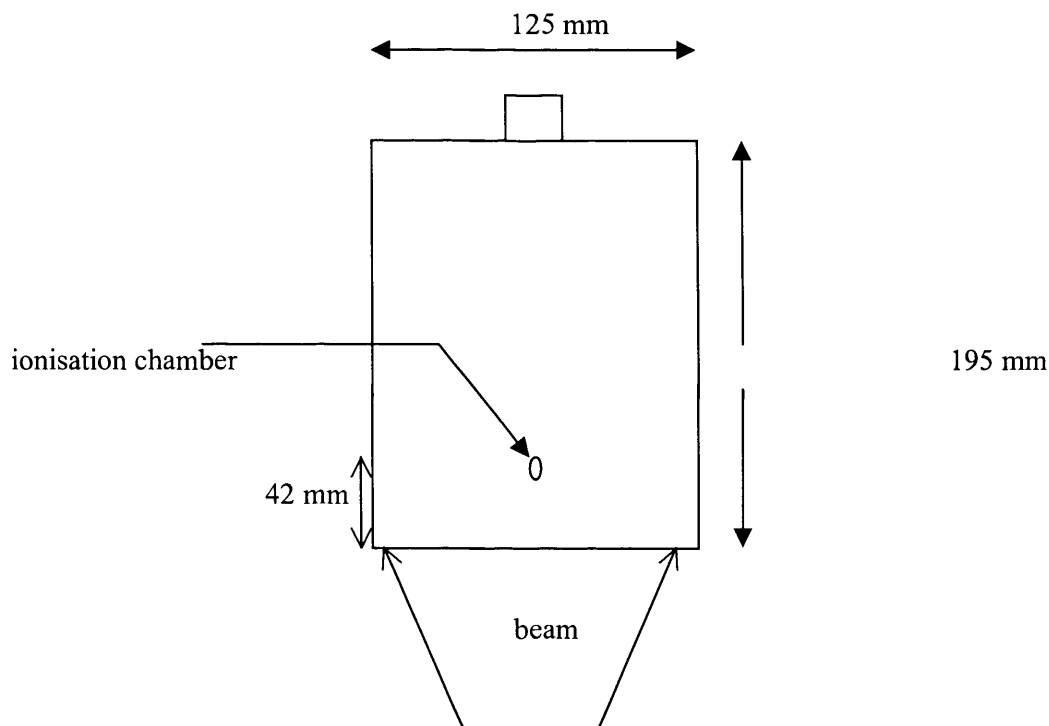


Figure 7.12 Cross-sectional view of the ion chamber position in the Barex phantom.

The phantoms were irradiated using 300kV x-rays from a Pantak DXT-300 orthovoltage x-ray machine [Pantak Inc., Connecticut, USA] with a filter of 0.8 mm Sn, 0.25 mm Cu, and 1.5 mm Al. During irradiation, WT1 tissue equivalent plastic sheets were placed on the top, bottom and on both sides of the phantom to ensure sufficient lateral scattering. The phantom was irradiated and imaged twice: first without an ionisation chamber or holder, and then with an ionisation chamber. The ionisation chamber used was an NE 258, A150

plastic wall Farmer. In both cases, an absorbed dose of 8 Gy was given at 5 cm of Perspex equivalent distance from the surface. A field size of 10×10 cm was used with the FSD of 50 cm. MR images were performed 1 day after irradiation with the slice thickness of 10 mm and in-plane resolution of 1.17 mm for MAGIC gel and slice thickness of 3 mm and in-plane resolution of 0.75 mm for PAG gel. Details of the MRI imaging and data analysis were described in sections 4.5 and 4.6. Depth dose curves were plotted from a central longitudinal slice and five pixels were averaged through the centre of the beam. Data was normalized at 20 mm depth from the surface. This depth was chosen to reduce any effect due to the phantom wall material near the surface.

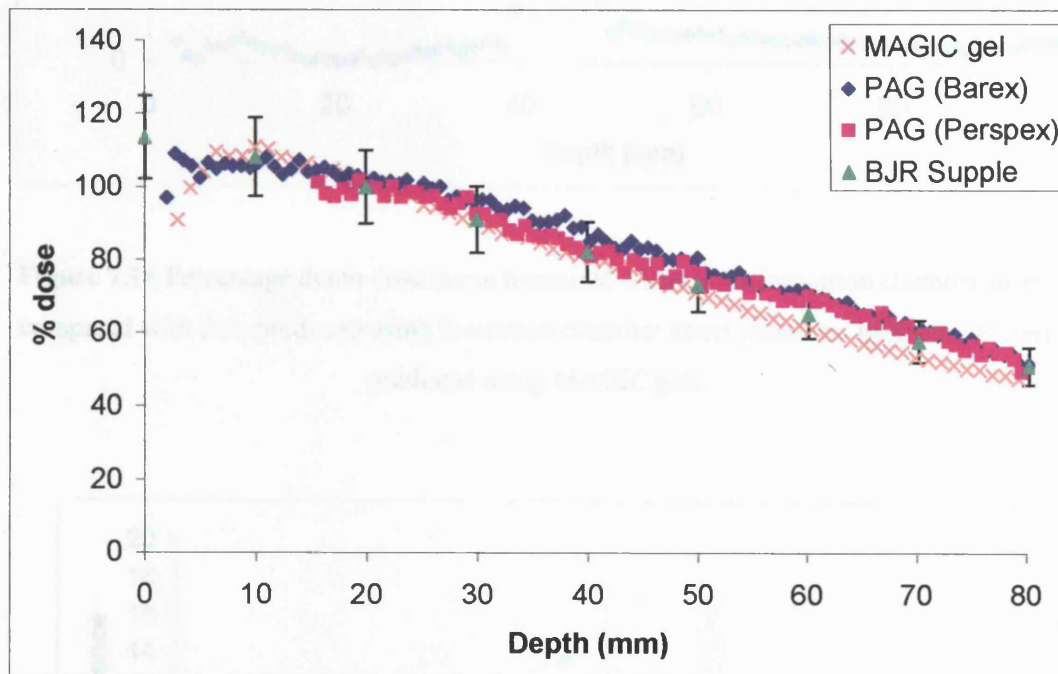


Figure 7.13 Percentage depth dose curve measured for 10×10 cm applicator for 300 kV x-rays and compared with BJR Supplement 17 [1983].

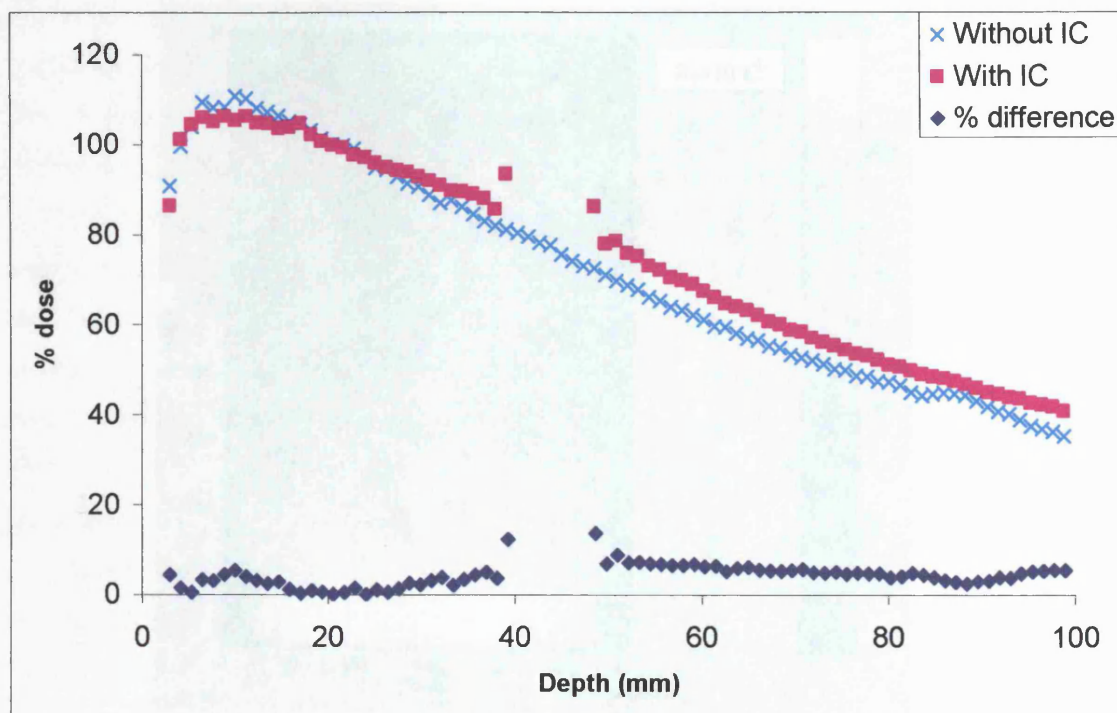


Figure 7.14 Percentage depth dose curve measured without the ionisation chamber insert, compared with data produced using ionisation chamber insert phantom. Both curves were produced using MAGIC gels.

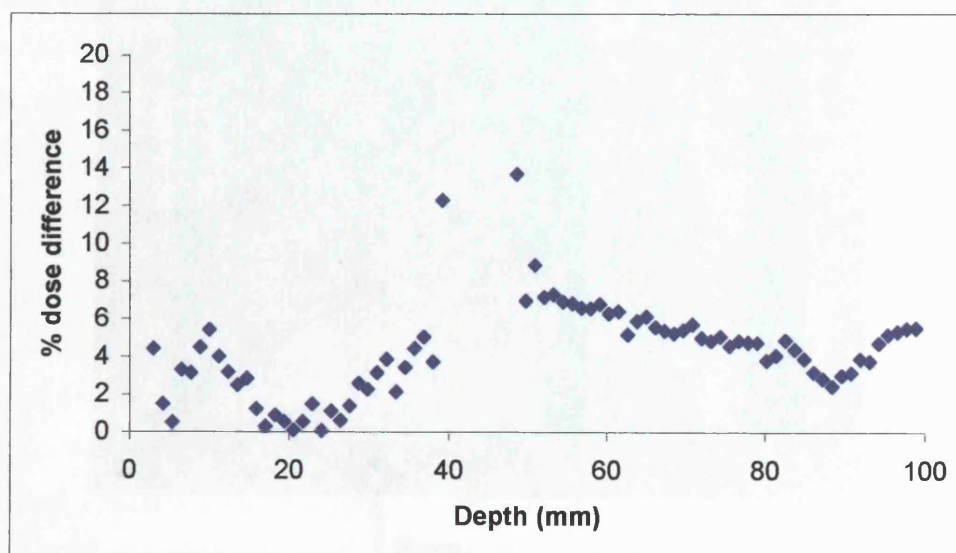
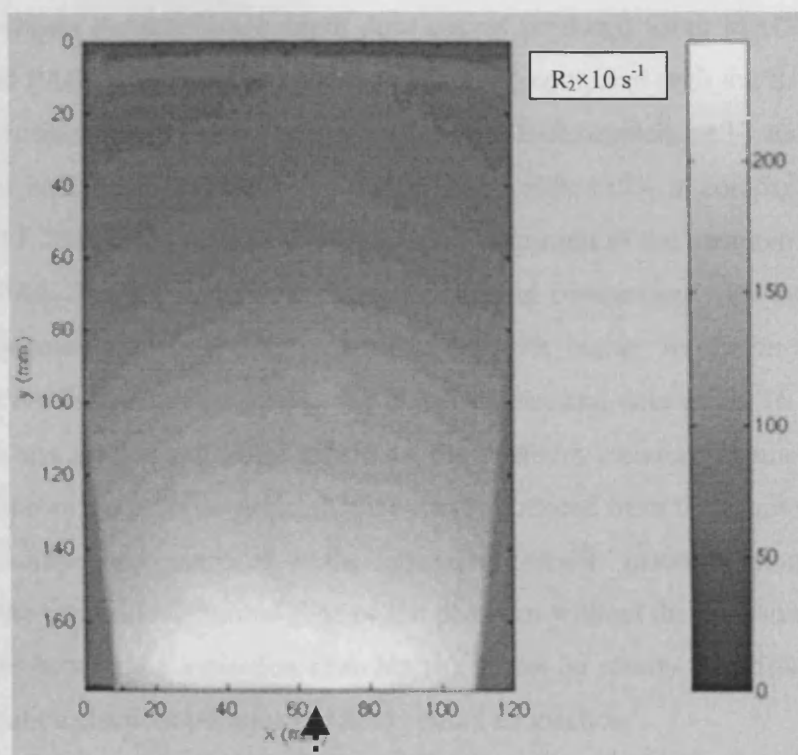
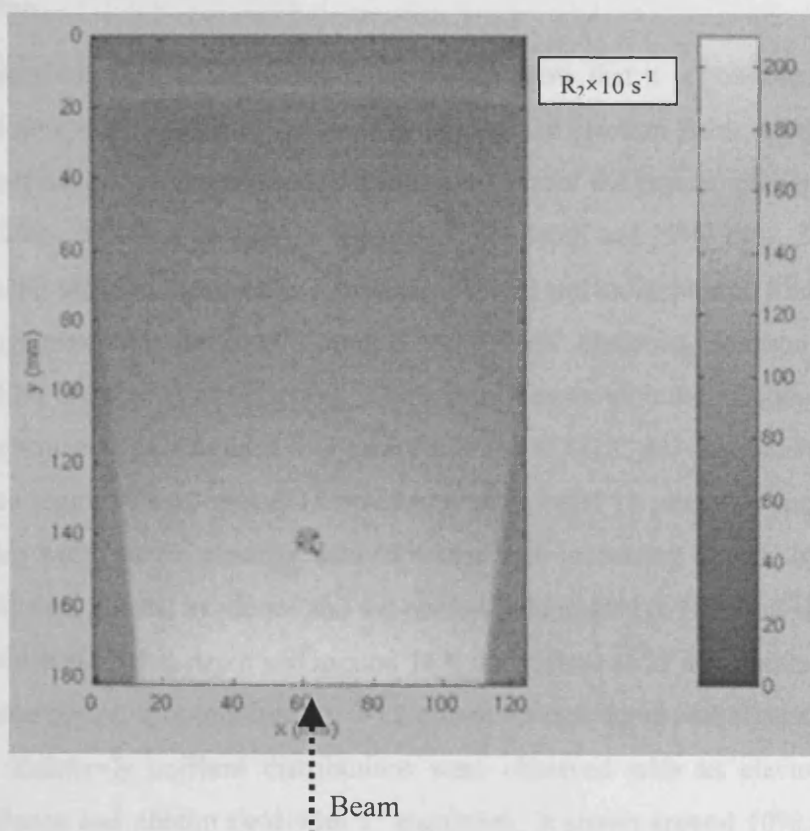


Figure 7.15 Difference between the two depth dose curves was shown in figure 7.14, with an expanded scale.



(a)



(b)

Figure 7.16 R_2 images produced using MAGIC gel at the centre of the x-rays beam: (a) without ionisation chamber insert and (b) with ionisation chamber insert.

Figure 7.13 shows the percentage depth dose curves produced using MAGIC gel (Barex phantom) and PAG (both Barex and Perspex phantom) compared with the BJR supplement data. It shows that there is a good agreement between BJR supplement 17 and MAGIC gel. PAG data for both Barex and Perspex phantom lies within $\pm 10\%$ in comparison with BJR supplement 17. The differences may be due to the distortion of the phantom at the time of irradiation. PAG data shows slightly more variation in comparison with the MAGIC gel data. This because the PAG data was measured with higher resolution and the SNR decreases as resolution increases. For the Perspex phantom, data up to 15 mm from the surface were not included to avoid effects of the phantom material [Bonnett et al 1999]. Figure 7.14 shows the percentage depth dose curve produced from the phantom without the ionisation chamber and compared to the ionisation chamber insert phantom data. Figure 7.16 shows the central longitudinal slice of the phantom without the ionisation chamber (a) and the phantom with the ionisation chamber (b). It can be clearly seen from both figures that the ionisation chamber perturbs the field behind its location.

7.6 Discussion

For matching photon and electron fields, the results show that it is possible to draw three dimensional dose distributions in the abutting photon and electron fields using hypoxic and normoxic polymer gel dosimetry. In the abutting region for the parallel photon and electron field, up to 20%, 20% and 26 % over dose at 15 mm depth and 19%, 28%, 26% over dose at 25 mm depth were recorded using PAG, MAGIC gel and radiochromic film respectively. Using radiographic film for 6 MV photon and 9 MeV electrons, Johnson et al [1994] reported a 20% hot spot at the junction. These results agree with their findings, although a different electron energy was used. For each PAG and MAGIC gel dosimeters the width of the over dose region is 8-10 mm at 15 mm depth and around 18 mm at 25 mm depth, since the penumbra width of the electron field increases with increasing depth. In contrast, the electron field with normal incidence and the photon field angled at 10° show maxima of 10-19% under dose at 15 mm depth and around 14% under dose at 25 mm depth. The width of the under dose region is approximately 9-12 mm at 15 mm depth and almost 15 mm at 25 mm depth. Relatively uniform distributions were observed with an electron field with normal incidence and photon field with 5° angulation. It shows around 10% under dose at 15 mm depth and 5-13 % over dose near the photon field and around 10% under dose near the electron field at 25 mm depth for each dosimeter, and the width of the over/under dose

region is 6-8 mm at 15 mm depth and 15 mm at 25 mm depth. Small variations were observed in each case, which might be due to positioning errors at the time of irradiation. In figures 7.3 and 7.7, profiles for the PAG shows a noisier signal than for the other profiles. This is because the resolution for these profiles was 0.75 mm, whereas the resolution for rest of the profiles, for both PAG and MAGIC gels was 1.17 mm and the signal to noise ratio decreases with improving image resolution.

Thesen et al [1995] reported 20-25% under dose for a 3 mm gap and 35 to 50% over dose for a 5mm overlap at 12 mm and 25 mm depth using 9MV photon beams and 8 to 10 MeV electron beams. This evaluation was performed by using an automatic video-densitometer and digital image processing. It was also reported that the dose inhomogeneity occurs at a width of 10 mm around the field margins. In this study, ~39% overdose at 15mm depth and 28-44% overdose at 25 mm depth were observed for 2 mm overlap between 6 MV photon and 12 MeV electron field. The dose inhomogeneities were observed around 8 mm at 15 mm depth and 16 mm at 25 mm depth. For a 2 mm gap approximately a 21% under dose at 15 mm depth and 9% overdose near the photon side and 10-19% under dose near the electron side at 25 mm depth were observed. This inhomogeneity occurs at a width of 20 mm around the field margin. The present results are similar to the findings of Thesen et al [1995], although different in magnitude, which is probably due to a different photon and electron energies and to different experimental setup.

Sometimes, small variations were observed between electron and photon profiles for both gels, and this probably due to the setup errors in the shape of phantoms. Here rectangular shaped Barex phantoms (wall thickness 1mm) were used. Due to its thin walls, after filling the phantom with gels, the top and bottom flat surface became bowed with a maximum displacement of approximately 8 mm.

Depth dose measurements for 300 kV x-rays were carried out using three different ionisation chambers by Aukett et al [1996]. They reported a maximum variation of 10.6% in comparison with BJR supplement 17 [1983]. In our study, depth dose curve measurement using MAGIC gel agreed well with BJR data. PAG gel data showed a small deviation (maximum 8% higher) from BJR data. This might be due to experimental setup

related error at the time of irradiation. The phantom used in this study whose dimension was $19.5 \times 12.5 \times 5.2$ cm., whereas an x-ray beam of 10×10 cm field size was used. The remainder of the area around the gel was covered using WT1 plastic equivalent sheet. The depth dose curve with the ionisation chamber insert shows significantly higher dose (up to 8%) behind the chamber in comparison with data without the chamber inserted. In figure 7.16b clearly shows that this difference is observed in a region only a few mm in width behind the chamber along the beam axis. This is due to the lack of radiation absorbed inside the chamber, since there is only air inside the chamber. Two points around the chamber shows relatively higher dose and this may be due to the magnetic susceptibility effects in the region of the air space.

Finally it can be concluded that PAG gel is energy independent for a range of commonly used electron and photon energies. At high doses there is the added complication of polymer saturation. These results also show that both types of gel are able to measure three-dimensional dose distributions in the junction of photon and electron field. Using polymer gel, it is possible to measure the perturbations created by an ionisation chamber.

Chapter 8

Conclusion and future work

8.1 Conclusions

The last few years have seen rapid technological developments in the field of radiotherapy. Treatment planning systems and radiation dose delivery are becoming increasingly complex with the emphasis on precise definition of target and highly sculpted dose distributions to spare nearby sensitive tissues. A significant challenge has arisen, however, because the rapid advances in the ability of technology to deliver complex radiation treatments have not been paralleled by corresponding developments in the ability to verify these treatments. A core issue is that different clinical treatments demand different specifications from a dosimeter. Brachytherapy utilizing low-energy gamma and high-energy beta sources, demands tissue equivalence and high spatial resolution. IMRT often requires high spatial resolution over large volumes. Radiosurgery demands still higher spatial resolution, and a higher dynamic range, but often over much smaller volumes. Existing dosimetric verification methods have proved more than adequate up to now, however, the limits of these one- and two-dimensional measuring devices are beginning to be reached. For this reason, there has been much interest in the development of a three-dimensional radiation-measuring device. Arguably, the PAG gel is probably the best dosimeter of this kind produced to date. This system is based on polymerisation and cross-linking of acrylic monomers in an aqueous gel by the action of radiation. These changes can then be measured using MRI or an optical CT scanner.

In gel dosimetry one of the most important factors is the manufacturing procedure of the gel. This together with the investigation of the main properties of the PAG dosimeter were described in chapter 4. This work has indicated that in order to produce a sensitive gel, the time of manufacture should be short and the last nitrogen purging period should be a minimum of 40 min. The manufacturing period can be reduced by reducing the time to dissolve the acrylamide and bis-acrylamide. This time can be reduced if the reaction flask is shaken after a few minutes. At the early stage of this work, the dissolving period was 70 min but by using a magnetic stirrer plus manual shaking, this time was reduced to 30 min. In the early stages the last nitrogen bubbling period was 30 min, this was increased to 40 min. Initially, the gel sensitivity was measured as $0.22 \text{ s}^{-1}\text{Gy}^{-1}$ but this was increased to $0.37 \text{ s}^{-1}\text{Gy}^{-1}$ by these simple improvements. After manufacture, the next most important stage is to transfer gel from the reaction flask to the phantoms or

calibration vials. Here, a simple pouring method was used, which is easier than other methods that have been used before. Some authors have recommended that the oxygen concentration inside the glove box should be less than 0.05%. In this study, it was found that an oxygen concentration of approximately 0.2% inside the glove box is sufficient to produce a gel with a high sensitivity. The time to eliminate oxygen from deionised water was also studied in this work and oxygen concentration was found to be reduced exponentially and to be a function of volume and flow rate as would be expected. This has not previously been quantified.

For the MRI measurements it was found that multi-echo and single spin echo sequences gave almost the same ~~dose~~-values of absorbed dose. If the availability of scanning time is a concern, it is recommended that a multi echo sequence be used as this will give good images within the shortest scan time. The gel was found to be quite homogenous after irradiation. A temperature increase of approximately 0.4 °C was observed inside RF coil during the scan for a approximately 10 min scan time.

Three different calibration methods were studied and Oldham's method [Oldham et al 1998b] was confirmed to be more accurate with a reduced standard error in comparison with the more common method using small vials of gel. The calibration method using a large phantom showed significant differences compared with the standard vial method.

The gel response was found to be linear within the lower dose region of 0 to 2Gy; this had not previously been quantified. It was confirmed that the decrease of dose sensitivity with temperature was $0.011 \text{ s}^{-1}\text{Gy}^{-1}$ per °C and a formula was used to calculate a temperature corrected dose image, which was used to measure an absorbed dose, which gave a closer value to the given dose.

This investigation has also given the first report of the use of calcium salt to make a bone equivalent gel with a density of 1.2 gm/cc. The response of this gel was found to be linear up to at least 10Gy but at higher densities the gel became liquid at room temperature.

An investigation of the main properties of the newly formulated MAGIC gel [Fong et al 2001] was described in chapter 5, and the different features of this dosimeter were investigated. The response of the gel to ionising radiation was found to be linear up to at least 50 Gy and linear in the lower dose region of 0 to 3Gy. Post manufacture, unirradiated MAGIC gels show a

continuous change in R_2 as do PAG. The gel response was found to increase with time as has been previously reported for the PAG. This study also highlighted that a single spin echo sequence gave a more sensitive result in comparison with multi-echo sequence. The gel can be used up to at least 14 days after manufacture and gives almost identical results over this period. One advantage of the MAGIC gel is that any phantom material can be used unlike other polyacrylamide gels. Dose overestimation at the edge of the irradiated region was observed for MAGIC gel similar to that seen in PAG. A decrease over time of area of the irradiated region was also observed in this study which had not been previously reported. This effect may be ignored if the gel phantom is scanned within 4 days of irradiation. The MAGIC gel response was found to show negligible energy dependence within the energy range of electrons and photons commonly used in radiotherapy. Depth dose measurement using MAGIC gel gave better results when compared to radiochromic HD 810 film. Measured electron energy using MAGIC gel showed good agreement with the electron energy measured using a parallel plate ionisation chamber. For MAGIC gels, the gel sensitivity and background R_2 were found to be dependent on the temperature at the time of the MR measurement. It was also found that the R_2 value depends on the temperature at the time of irradiation; this has not previously been reported for any polymer gels. Initial results of depth dose distributions showed good agreement between the gel and the planning distribution. Initial measurements of absolute dose show good agreement with prescribed dose. The maximum variation was observed to be $\pm 3.4\%$, achieved by maintaining the same temperature for calibration vials and phantoms at the time of irradiation and MR measurement. In the early stages of the study, gel fogging was observed within two hours of manufacture and a polymerised area was seen a few days after manufacture at the top of the phantom. This may have been due to the initial lack of temperature control at the time of preparation. Currently, no gel fogging or polymerised area is observed. A brief comparison between PAG and MAGIC gels is given in Table 8.1.

It is concluded that the MAGIC gel has more advantages than the PAG and would be the dosimeter of choice providing the possible decrease in the irradiated area and the temperature dependence at the time of irradiation are taken into account.

After successfully improving the manufacturing technique of the PAG dosimeter and having confirmed the main properties, the gel was used for measurements in cardiovascular brachytherapy. The results in chapter 6 indicate that PAG dosimeters can be used to measure the

dose distributions specified by the AAPM for vascular brachytherapy sources by using high resolution MRI, and that more complex geometries can be investigated in the future.

Characteristics	PAG	MAGIC
Linearity	0 - 10 or 12 Gy	0- 50 Gy
Sensitivity	0.22 to 0.37 s ⁻¹ Gy ⁻¹	0.6 to 0.66 s ⁻¹ Gy ⁻¹
Back ground R ₂	1.16 to 1.5 s ⁻¹	3.0 to 5.2 s ⁻¹
Manufacturing time	approximately 3 h	approximately 1.5 h
Manufacturing system	Difficult	Simple
Gel cost (chemicals only)	~£35 /litre	~£20/litre
Toxicity	Neurotoxic (acrylamide), bis-acrylamide also toxic	Hydroquinone and methacrylic acid is less toxic than acrylamide and bis-acrylamide
Energy dependency	Independent (commonly used energy range of electron and photon)	Independent (commonly used energy range of electron and photon)
Absolute dose measurement	±6%	±3.4%
Phantom material	Glass and Barex™	Glass, Barex™, Perspex, PVC etc.

Table 8.1 Comparison between PAG and MAGIC gels.

For most measurements an in-plane resolution of 0.4 mm, with an imaging time of approximately 1 hour would appear to be sufficient for measurements of vascular brachytherapy sources. If a higher resolution of 0.2 mm is used, then the results show more variation in the absorbed dose profiles and this requires further investigation. The spatial resolution achievable in an MR imaging system depends fundamentally on the strength of the magnetic field gradient used for localisation. However, in practice, the technique is SNR limited, and the SNR is determined by two factors: the strength of the static polarising magnetic field, and the time available for scanning. Approximately, for constant SNR, the linear size of image pixels is proportional to the field strength raised to the power $-1/3$, and proportional to the scanning time to the $-1/6^{\text{th}}$ power. With the relatively high field strength used in our study, we were able to achieve in-plane

resolution of down to 0.2 mm, with slice thickness of 0.5 mm. However, this required long scan times in order to achieve good SNR. The strength of the relationship between resolution and scan time shows that with only slightly poorer resolution, more acceptable scan times of around 1 hour would give adequate resolution for scanning intravascular brachytherapy dosimeters. This technique is however restricted to centres with access to high resolution MRI, which is an obvious disadvantage. A further disadvantage is the process required to manufacture the gel with all the stringent requirements to exclude oxygen, however some gels are commercially available. On the other hand radio-chromic film is readily available and requires the use of a relatively inexpensive densitometer. These investigation indicates that MD-55 would be the dosimeter of choice and that whilst it would be difficult to measure radial distributions it would be the method of choice for the measurements of absorbed dose distributions parallel and orthogonal to a source train used for intravascular brachytherapy.

It has been shown in chapter 7 that the PAG gel response is energy independent for the commonly used photon and electron energies for radiotherapy at least up to 6 Gy. Both PAG and MAGIC gels were used for measurements of dose distributions in the abutting photon and electron fields, with results that were quite encouraging. Some small variations were observed between electron and photon profiles for both gels, possibly due to set-up error or to the shape of the phantom. It should be noted that Barex sheet of 1 mm thickness was used to construct the rectangular shaped phantom, and after filling with gel the top and bottom flat surface of the phantom became bowed and an improved design of phantom is needed. In this study, radio chromic film also used to measure profiles in the junction region. The more obvious advantages of the gel are: its three dimensional nature, being the dosimeter as well as the phantom and its ability to take any configuration depending on the shape of the container. From the 300 kV x-rays study it can clearly be seen that using polymer gel it is possible to measure the perturbations caused by an ionisation chamber within the field.

The main disadvantage of gel dosimetry is that it cannot measure absolute dose with great accuracy. In this study, using MAGIC gel and controlling the temperature of both calibration vials and phantoms at the time of irradiation and MR measurement, absolute doses were measured with a variation within $\pm 3.4\%$. Using PAG gel, it was possible to keep differences between measured dose and prescribed dose to approximately $\pm 6\%$. Measurements with MAGIC gels show a promise for absolute dose measurement. Further investigation is needed for the absolute dose measurement with PAG. In particular the differences on dose sensitivity between large phantoms

and small calibration vials, together with the effects of temperature control at the time of gel manufacture.

8.2 Further work

The work presented in this thesis provides improved techniques for the manufacture of PAG and MAGIC gels. Basic information on the main properties of both types of gel have also been confirmed and reported, and some practical aspects of their applications in different areas of radiotherapy have been highlighted. However there is still scope for considerable further work.

Absolute dose measurement is still a debatable issue for both types of gels. This work indicates that polymer gels will remain a relative dosimeter, but MAGIC gels show improved accuracy and should be investigated further. The differences in calibration results for small vials and large phantoms using PAG have still not been adequately explained, and further investigation is needed. Investigation of basic MRI properties of MAGIC gels is now complete, but further investigations are essential for MAGIC gels, particularly for use with optical CT scanners, and spectroscopic techniques. Only PAG has been applied to vascular brachytherapy here, and it would also be of interest to see how suitable MAGIC gels are in brachytherapy. Preliminary results for vascular bifurcation and stent phantoms have been reported and more investigations are needed. In this study abutting photon and electron field has been studied using a rectangular shaped phantom. The results would be more realistic if a head and neck phantom could have been used to study the abutting photon and electron field. In this work, bone equivalent gels were prepared with density of 1.2 g/cc. Further investigation is needed to make bone equivalent gel with density up to 1.8 g/cc for realistic bone simulation, so that a truly anthropomorphic phantom can be constructed. It is clear that methods of three-dimensional measurement of absolute dose are needed for the quality control of future radiotherapy treatments and further investigations into dosimeter materials are required, but it is obvious that methods, which do not depend on equipment with limited availability, are advantageous to the radiotherapy centre.

Chapter 9

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