UNIVERSITI PUTRA MALAYSIA

PREPARATION OF N-ISOPROPYL ACRYLAMIDE POLYMER GEL DOSIMETERS AND THEIR CHARACTERIZATION BY RAMAN SPECTROSCOPY

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By

MOHD ZULFADLI ADENAN

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

November 2014

To:

My parents and family, they are my beloved father Adenan bin Misron and mother Arbaidah binti Utoh , as well as my beloved wife Wan Norbaizura binti Wan Ismail and my kids Muhammad Akram Majdi and Muhammad Asim Muzakkir

Thanks for the encouragement, sacrifice, love and support given

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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MOHD ZULFADLI ADENAN

November 2014

Chairman : Professor Elias Bin Saion, PhD

Faculty : Science

This present work aims to synthesise N-isopropyl acrylamide (NIPAM) polymer gel and study the effect of NIPAM monomer and N, N'-methylene-bisacrylamide (BIS) crosslinker concentrations on polymerization of NIPAM polymer and NIPAM and BIS consumptions in gelatin matrix induced by gamma rays at dose between 0 and 21 Gy. The NIPAM polymer gels were synthesized from NIPAM (2 to 4% w/w) and BIS (2 to 4% w/w), gelatin (6% w/w), anti-oxidant tetrakis hydroxymethyl phosphonium chloride (THPC) (5 mM), and de-ionized water. The samples were irradiated with ^{60}Co Gamma cell instrument at a constant dose rate, receiving doses from 3 Gy up to 21 Gy. The dose response of irradiated NIPAM polymer gel was determined using Raman spectroscopy.

Raman peak intensities were identified in the samples at 815 cm^{-1} assigned bonding for C-C of NIPAM polymer gel, 1025 cm^{-1} assigned bonding for C=C of NIPAM and 2353 cm^{-1} bonding for C=C of BIS. The Raman intensity y that corresponds to the rate of polymer formation in NIPAM polymer gel increases with increasing dose D and fitted with the monoexponential equation $y = y_0 + A(1 - e^{-D/D_0})$. The dose sensitivity D_0 derived from the equation that was also found increasing with the increase of initial concentrations of NIPAM monomer and BIS crosslinker. The rate of co-monomer consumption decreases with increasing dose and was fitted with the monoexponential equation $y = y_0 - A(1 - e^{-D/D_0})$. The dose sensitivity D_0 were also found to increase with the increase of initial concentrations of NIPAM monomer and BIS crosslinker.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Sarjana Sains

PENYEDIAAN N-ISOPROPIL AKRILAMIDA DOSIMETER POLIMER GEL DAN PENGUKURAN DENGAN RAMAN SPEKTROSKOPI

Oleh

MOHD ZULFADLI ADENAN

November 2014

Pengerusi : Profesor Elias Bin Saion, PhD

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Kajian ini bertujuan untuk mensintesis polimer gel N-isopropil akrilamida (NIPAM) dan menganalisa tindakbalas kepekatan monomer NIPAM dan penyilangjalin N, N'-metelin-bisakrilamida (BIS) ke atas proses pempolimeran polimer NIPAM dan juga penggunaan NIPAM dan BIS di dalam gelatin yang ditindakbalaskan dengan sinaran gamma pada dos daripada 0 hingga 21 Gy. Polimer gel NIPAM telah disintesiskan daripada NIPAM (2 to 4% w/w) dan BIS (2 to 4% w/w), gelatin (6% w/w), agen anti-oksida tetrakis hidroksimetil fosfonium klorida (THPC) (5 mM) dan air ternyah ion. Sampel-sampel ujikaji telah didedahkan dengan sinaran radiasi oleh instrumen gamma sel pada kadar yang tetap, dengan menerima dos daripada 3 Gy hingga 21 Gy. Hasil tindakbalas daripada pendedahan sinaran radiasi ke atas polimer gel NIPAM ditentukan dengan menggunakan Raman spektroskopi.

Tiga intensiti puncak telah dikenalpasti pada 815 cm^{-1} yang mewakili ikatan C-C kepada polimer gel NIPAM, 1025 cm^{-1} yang mewakili ikatan C=C kepada NIPAM dan 2353 cm^{-1} yang mewakili ikatan C=C kepada BIS. Intensiti Raman *y* yang berhubung dengan kadar pembentukan polimer di dalam polimer gel NIPAM meningkat dengan peningkatan dos *D* dan menepati ungkapan monoeksponen iaitu $y = y_0 + A(1 - e^{-D/D_0})$. Sensitiviti dos D_0 yang dijelmakan daripada ungkapan juga menunjukkan peningkatan seiiring dengan perubahan kepekatan kepada monomer NIPAM dan penyilangjalin BIS. Kadar penggunaan monomer NIPAM dan penyilangjalin BIS menunjukkan penurunan dengan peningkatan dos dan menepati ungkapan monoeksponen iaitu $y = y_0 - A(1 - e^{-D/D_0})$. Sensitiviti dos D_0 juga menunjukkan peningkatan dengan peningkatan kepekatan monomer NIPAM dan penyilangjalin BIS.

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May Allah bless and reward them all. Ameen.

This thesis submitted to the senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

THPC	tetrakis hydroxymethyl phosphonium chloride
BIS	N, N'-methylene-bisacrylamide
NIPAM	N-isopropyl acrylamide
THPC	tetrakis hydroxymethyl phosphonium chloride
MAA	methacrylamide
AA	acrylamide
MAGAT	methacrylic acid, gelatin and THPC
PAGAT	polyacrylamide gel, gelatin and THPC
PAG	polyacrylamide gel
MAG	methacrylic acid gel
BANG	bis-acrylamide, acrylamide, nitrogen, gelatin
MAGIC	methacrylic and ascorbic acid in gelatine initiated by copper(II) sulphate, ascorbic acid and hydroquinone
HEA	hydroxyethylacrylate
PHEA	polyhydroxyethylacrylate
Gy	Gray (radiation dose unit)
a.u.	arbitrary unit
A	atomic mass
NMR	nuclear magnetic resonance
MRI	magnetic resonance imaging
CT	computed tomography
R	relaxation rate of magnetic resonance
D	absorbed dose

$D0$	dose sensitivity
ϕ	particle fluence
v	frequency
γ	gamma ray
h	Plank's constant
IMRT	intensity modulated radiotherapy
SRS	streotactic radiosugery
SRT	Stereotactic radiotherapy
λ	wavelength
μ	linear absorption coefficient
μ/ρ	mass absorption coefficient
ρ	density of dosimetry solution
T2	spin-spin relaxation rate
σ	cross-section
ΔA	change in absorbance at peaks
3D	three dimensions
TE	tissue equivalent

CHAPTER 1

INTRODUCTION

1.1 Radiation dosimetry

Radiation dosimetry can be defined as the science or technique of determining absorbed dose of ionizing radiation in materials especially human tissues. This may involve measuring the quantity of dose known as dose assessment which includes the measurements and calculations of dose in tissue substitutes (NCRP 2011). It is very crucial to ensure that this particular science and technique must be developed from time to time which otherwise harmful to radiation workers if the management of dose is not properly observed.

A device that can quantify the amount of dose is addressed as a radiation dosimeter. This device demonstrates a change in physical properties such as heat, charge, voltage, resistance, and luminescent or chemical properties such as radiographic contrast, ions formation and chemical bonding of irradiated materials which is proportional to the net amount of dose. The phenomenon of radiation imparting some or all of its energy to the material it passed is termed as absorption. The absorption of ionizing radiation is the absorbed dose that is defined as the mean energy imparted in the irradiated medium per unit mass.

There are two types of dosimeter which are physical and chemical dosimeters. For the physical dosimeter, it involves basic physical changes for measuring absorbed dose, such as a number of ion-electron pairs in ionization chambers. The chemical dosimeter is referred to a dosimetry system that upon irradiation, there is measurable change in its chemical properties, such as formation of ferric ions from ferrous ions in Fricke dosimeter (Izewska and Rajan, 2005). One of this chemical dosimeter is applied for calibrating Intensity Modulated Radiotherapy (IMRT) that need verification of three-dimensional (3-D) dose distribution. Another chemical dosimeter known as a polymer gel dosimeter has been developed which is capable of measuring 3-D dose distribution (De Deene et al., 2002a).

A radiotherapy treatment system utilises ionizing radiation either as a primary treatment or as part of a treatment regime for cancer that may include surgery, chemotherapy, hormone therapy to control malignant cell growth. The aim of radiotherapy may be curative, with the disease being irradiated and cure achieved. The scope of radiotherapy includes adjuvant treatment to keep cancer from returning, neo-adjuvant treatment to shrink a tumour before the main treatment (typically surgery), or palliative treatment for local disease control and symptomatic relief in the cases where cure is not possible (Khan and Gerbi, 2011).

Furthermore, as the radiation energy is imparted, it may result in ionization and excitation of atoms or molecules. In particular, there are several consequences that occur in the chemical dosimeter upon irradiation. First, once the radiation energy is absorbed by the chemical dosimeter, it triggers the bounded and free electrons to be ejected and produced ions and free radicals, which may promote subsequent chemical reactions. Radiolysis of water results the formation of hydrogen, (H^+) and hydroxyl (OH^-) as well as chemically reactive uncharged free radicals of hydrogen, ($H^\bullet$) and hydroxyl ($OH^\bullet$) (McJury et al., 2000). Next, series of events may take place that end up of subsequent chemical reactions, such as polymerization and crosslinking (Turner, 2005).

A chemical dosimeter is based on chemical reactions that capable of measuring dose after interacting with ionizing radiation. The dosimeter should be accurate and reliable and its calibration should be in line with the national and international standard. Historically, the first chemical dosimeter introduced, which is Fricke dosimeter containing ferrous sulphate solution, which changed to ferric sulphate from the radiation-induced oxidation process of ferrous sulphate solution. As a point dosimeter it has certain limitations. Incorporating with gelatin, the Fricke dosimeter improved its capability to become tissue equivalent (TE) material and perform 3-D dosimeter for the first time after incorporating with CT scanner or MRI scanner (Baldock et al., 2001). The Fricke dosimeter has been claimed as a basic and standard dosimeter, since it fulfils most of the dosimeter standard features. Based on the theory, the ideal and good dosimeter must meet all of these following requirements:

a) High accuracy and precision
b) Linearity of signal with dose over a wide range
c) Small dose and dose rate dependence
d) Flat energy response
e) Small directional dependence
f) High spatial resolution

However, the diffusion of ferric ions into non-irradiated regions is the main problem of Fricke gel dosimeter and limits the accuracy of this dosimeter for clinical application (Baldock et al., 2010). This may be resolved by the introduction of polymer gel dosimeters, a potential 3-D dosimeter, which are based on the chemical reactions of co-monomers into long chain polymer fixed in gelatine, a tissue equivalent (TE) material.

An ideal dosimeter must be independent of dose rate, in which the dosimeter is not really sensitive with the different dose rate. Therefore, the measurement must be constant, when different dose rates are being applied, and the dosimeter only responses with different amount of net absorbed dose. In real practice, this is not possible to achieve, thus requires the dosimeter to undergo certain correction and calibration procedures.

1.2 Polymer gel dosimeter

There are many studies which emphasize on 3-D polymer gel dosimeters of choice, due to their tissue equivalent characteristic for clinical radiotherapy and radiation oncology. The main objective of radiotherapy is to irradiate the specific organ or tissue by destroying the cancerous cells, but spare the normal healthy tissue within the surrounding (Søndergaard et al., 2009). The outcome of the treatment is whether to cure or just to reduce the severity of the cancers. The radiation given is expected to change chemically and biologically of the target cancer cells in tissues or organs.

Polymer gel dosimeters must be accurate as possible, in which the mean value has a very small difference as compared to the true value. Precision of dosimeter refers to the degree of reproducibility of a dosimeter measurement, in which every measurement done, if all value is similar or nearly similar, the dosimeter is considerably high precision. Uncertainty is the term referred to accuracy and precision applied in measurements. The dosimeter must be linear or directly proportional to the dosimetric quantity, for example, the optical density versus absorbed dose. The pattern of measurement should be, as the dose increases, so the optical density also increases in a straight and proportional line form.

The response of dosimetric system is a function of the radiation energy. The measurement of dosimeter also must have identical response with the same radiation energy or quality. Correction of measurement must be taken, if the response of the applied beam quality is not identical to the calibration beam quality. Then, the dosimeter needs to have small directional dependence, in which it is less sensitive with a physical size of dosimeter. A good dosimeter, must have high spatial resolution, where certain area in the composition of polymer gel dosimeters, has absorbed certain amount of dose that depicts specific measurement to the effective point of measurement (De Deene, 2004).

Many studies have stressed on a need of dosimetric system which able to quantify absorbed dose in 3-D since the development of complex radiotherapy treatment that applied higher amount of dose and multi-direction of beam. For instance, a procedure in IMRT must have complete verification of 3-D dose profile, due to dynamic treatment that applied multi-direction of radiation beam (Wuu and Xu, 2006). Therefore, polymer gel dosimetry should fulfil the requirement of 3-D dose verification by determining high spatial resolution of 3-D dose distribution prior to the actual radiotherapy procedure.

Polymer gel dosimeter studies were first based on the molecular weight compounds of acrylamide (AA) as a monomer and N-N'-methylene-bisacrylamide (BIS) as a cross-linker in gelatine and become polyacrylamide when irradiated with ionizing radiation. This new type of polymer gel dosimeters has replaced the Fricke-gel dosimeter (Maryanski et al., 1993). There are many formulations of polymer gels

have been tested previously including BANANA (BIS-acrylamide, Acrylamide, Nitrous oxide, and Agarose), BANG-1 (BIS-acrylamide, Acrylamide, Nitrogen, Gelatin) (Maryanski et al., 1993, Maryanski et al., 1994), BANG-2 (BIS-acrylamide, Acrylamide, sodium hydroxide, Nitrogen, Gelatin) (Maryanski et al., 1996a), BANG-3 (BIS-acrylamide, methacrylic acid, sodium hydroxide, Nitrogen, Gelatin), PAG (Polyacrylamide Gel) (Baldock et al., 1998), VIPAR (N-vinylpyrrolidone-argon based) (Kipouros et al., 2001) as well as HEA (2-hydroxyethyl acrylate, bis-acrylamide, acrylamide, gelatin) (De Deene et al., 2002a). The main idea is that, different monomers result different formulation of polymer gel dosimeters.

1.3 Problem statement

New radiotherapy techniques such as stereotactic radiotherapy (SRT) and stereotactic radiosurgery (SRS) aim to deliver a high dose to the soft tissue or target organ while sparing the surrounding normal healthy tissues. Due to these complicated treatment techniques, there is a need for a high accuracy of dose verification system. Polymer gel dosimeter incorporated with nuclear magnetic resonance imaging (MRI) is one of the accurate and suitable means to measure radiation dose in 3-D dose distribution and can be used to simulate the radiotherapy condition.

The new normoxic polymer gel dosimeter is based on N-isopropyl acrylamide (NIPAM) as the monomer and N, N'-methylene-bisacrylamide as the crosslinker has been introduced (De Deene et al., 2006, Senden et al., 2006), which reduces toxicity of chemicals used and easy preparation compared with normoxic polyacrylamide gels (nPAG). The introduction of NIPAM polymer gel dosimeter, is considered as an alternative to previously used polymer gel dosimeters because NIPAM monomer has lower toxicity and the dose sensitivity is comparable to the previous polymer gels (Senden et al., 2006). However, most investigation on NIPAM polymer gel dosimeters have been studied entirely using nuclear magnetic resonance imaging (MRI) or computer tomography (CT) scan. MRI is directly based on the relaxation time of protons of water in the matrix of polymer gel dosimeters (Shani, 2000). As such, it is indirectly measured the polymerization of co-polymers of polymer gel dosimeters induced by ionizing radiation. While, CT scan is directly related to the radiation attenuation coefficient of matters, which is atomic number dependent (Bushberg, 2002). However, the Raman spectroscopy, on the other hand, is directly measured the covalent bonds present in the polymer gels, which is the correct method in quantifying the amount of polymerization and the consumption of co-polymers of NIPAM polymer gel dosimeters. Thus, the Raman spectroscopy will be used entirely to study NIPAM polymer gel dosimeters synthesized for this work.

1.4 Objective of study

The aims of this study are summarized as follows:

a) To prepare low toxic N-isopropyl acrylamide (NIPAM) polymer gel dosimeters for usage in simulation of radiotherapy dosimetry.
b) To evaluate the rate of polymerization (polymer formation) of NIPAM polymer gels by using Raman spectrometer.
c) To evaluate the rate of consumptions of co-monomers (monomer and cross-linker) of NIPAM polymer gels by using Raman spectrometer.
d) To investigate the dose sensitivity and half dose of NIPAM polymer gels.

1.5 Significance of study

The TE polymer gel dosimeters have been fabricated as a tool to measure and verify 3-D dose distributions of radiation beam used for radiotherapy treatment (Baldock et al., 2010). In reality, most of the researchers have been trying to discover new monomers with lesser toxicity and higher sensitivity, which is one of the obstacles, in the other polymer gel compositions (Ghavami et al., 2010). In addition, the polymer gel dosimeter that has certain unique advantages and TE characteristic that is similar to human tissue can be tested and applied in the simulation of radiotherapy procedure with no limitation (Novotný Jr et al., 2002).

Some of previous researchers claim that it is crucial to apply less toxic of dosimeter with more simple preparation, in which, chemical known as N-isopropyl acrylamide (NIPAM) is a chemical of choice with lower toxicity and prepared under normal atmosphere with no glove box by addition of anti-oxidant agent in the composition (Pappas et al., 2001, Senden et al., 2006).

The significant of this study is to further investigate NIPAM polymer gel, prior to the application in the clinical radiotherapy treatment, by evaluating the rate of polymer formation and rate of co-monomers consumption, which is directly characterized by Raman spectrometer based on the interaction of radiation with NIPAM polymer gel.

1.6 Outline of the thesis

This study is structured as follows:

Chapter 2 is about literature review which describes general information and history of gel dosimeter, advantages, types, anti-oxidant agent, polymerization process, linearity of gel dosimeter and finally toxicity issue.

Chapter 3 is about theoretical background of this study including, types of ionizing radiation, effects of radiation, types of radiation interactions with matter, absorbed radiation dose of dosimetry and Raman scattering theory.

Chapter 4 is about the preparation of NIPAM polymer gel, irradiation set up by using gamma cell instrument, measurement set up by using Raman spectrometer.

Chapter 5 is a discussion in details on experimental finding with respect to the measurement of Raman scattering. At the end, Chapter 6 describes summary of this study and suggestions for future work.

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