Mini Review
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# Three dimensional radiochromic detection of therapeutic radiation

## Abstract

Advances in radiotherapy over the last twenty years have resulted in the ability to deliver complex therapeutic treatments. Radiation oncologists can deliver complex treatment modalities designed to maximize irradiation of the tumor mass while limiting the exposure of proximal normal tissues. The planning of the radiotherapy treatment is essential to a successful clinical outcome. Recently three-dimensional dosimetry has enabled the testing and verification of calculated therapeutic radiation protocols, in which the clinician can visualize the impact of the proposed therapy on dosimetric media simulating the tissue and tumor mass of the patient. Here in the development of a solid plastic dosimeter, which can accurately and quantitatively report the field and intensity of radiation, is discussed. This dosimeter holds great promise to assist radiation oncologists to fine-tune and validate proposed radiotherapy treatments.

**Keywords:** polymers, radiation, leuco dyes, triarylmethanes

Volume 2 Issue 2 - 2018

John A Adamovics
Department of Chemistry, Rider University, USA

**Correspondence:** John A Adamovics, Department of Chemistry, Rider University, 2038 Lawrenceville Road, Lawrenceville, NJ 08648-3099, USA, Email jadamovics@rider.edu

**Received:** March 03, 2018 | **Published:** March 26, 2018

## Introduction

The global burden of cancer is increasing at an alarming rate and presents a major health challenge with 14 million new cancer cases expected to be diagnosed yearly.[1] Approximately fifty percent of all cancer patients can benefit from radiation therapy in the management of their disease. Over the last decade radiation therapy has developed from simple two dimensional to four dimensional techniques.[2]

Because radiation affects normal tissues and tumors, achieving an acceptable therapeutic ratio requires that the radiation dose be delivered with a high level of control of precision, accuracy, and intensity. This places great demands on the radiation therapy equipment. Inconsistencies in planned and delivered treatment can lead to serious complications if too much radiation is delivered, while too little radiation can result in ineffective tumor control. Correspondingly, there are stringent requirements on the tools used to measure radiation dose distributions. From the outset of the planning stages and continuing through to the completion of the radiation treatment delivery, a comprehensive quality assurance (QA) regime is required in radiotherapy in order to achieve an effective and safe treatment.[3] QA methods are necessary to determine the difference between calculated and actual dose distributions. Although inadequate for most 3D radiation treatments, 2D radiochromic film, in which color is formed upon exposure to ionizing radiation, has been frequently used for this determinations.[4]

The ideal 3D dosimeter, first proposed in 1961, should be firm in structure, and tissue equivalent.[5] This review describes the development of a 3D dosimeter, first introduced in 2004, which is composed primarily of polyurethane containing a radiochromic leuco dye[6] and fulfills those requirements.

## Leuco dyes

It was clear early on that the solid dosimeter should incorporate a reporter molecule which did not appreciably absorb light in the visual spectrum when formulated within the polyurethane matrix, but which, after exposure to ionizing radiation, would absorb light at frequencies within the visible spectrum, thereby imparting quantifiable color to the irradiated volume. Leuco dyes, which may exist in a colorless form, but which can transform, through one- or two-electron oxidation processes, to a colored variant, seemed well-suited for the purpose.[7]

After extensive experimentation, it was found that triarylmethane leuco dyes could be formulated into colorless transparent dosimeters which, upon irradiation, exhibited the desired color transformation. The colored region within the irradiated dosimeter accurately measured the radiation field and intensity of radiation dose, and proper scanning techniques could return a 3D image of the applied radiation field. The well-known leucomalachite green (LMG) 1 was initially studied. This dye has been widely utilized.[7] Other related leuco dyes were investigated for their effectiveness in this application.[8] The ability of 4,4'-(bis) N,N-dialkyl triarylmethanes (DTBs) such as LMG to form stable colored radicals in solution has been reported.[9] Several triarylmethane variants were prepared and formulated in a solid polyurethane matrix and evaluated for their ability to produce acceptable color changes upon irradiation, and were rated relative to LMG and reported as Relative Radiation Dose Sensitivity (Table 1).

TAMs have been traditionally prepared by acid promoted Baeyer condensation of two equivalents of N,N-dialkyl aniline with an equivalent of aryl aldehyde, exemplified by the synthesis of LMG (Figure 1).[10]

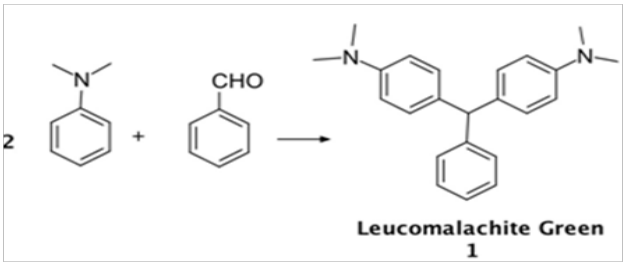


**Figure 1** Acid catalyzed synthesis of leucomalachite green (LMG).

In order for the dosimeter to be reactive to clinical radiation doses a radical initiator must be formulated with the DTB[8] It was found that tetrahalomethanes were efficient initiators. Dose sensitivity

 

of formulations of a given DTB depended upon the nature of the tetrahalomethane, with $CI_4 > CBr_4 > CCl4$.[11,12]

The goal of producing a clear solid dosimeter was achieved by blending the DTB and initiator in a plastic matrix. Transparent polyurethane was found to be ideal since the rate of polymer curing can be controlled by varying temperature, total volume of the reactants, and type and concentration of metal catalyst. Metallic catalysts, typically dibutyltin dilaurate or phenyl mercuric acetate accelerate the polymerization of an aliphatic isocyanate, typically bis(4-isocyanatocyclohexyl) methane (HMDI) and polymeric polyols, usually polyethers or polyesters, to form transparent polyurethane.[13] Sixteen DTBs, with a controlled quantity of tetrabromomethane were formulated in polyurethane using this process. The formulations were then evaluated for their response to a clinically relevant radiation dose (Table 1).

**Table** Synthesized DTBs and their LMG (1) relative radiation dose sensitivity (RRDS)

| DTB | RRDS | DTB | RRDS | DTB | RRDS | DTB | RRDS |
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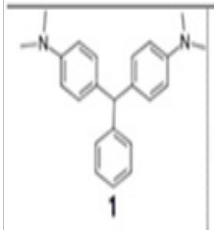
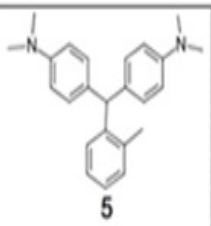
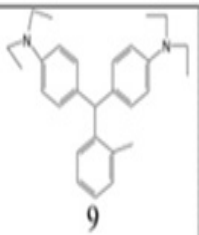
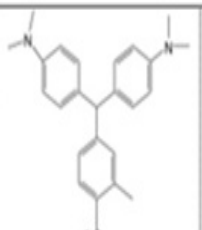
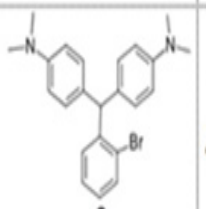
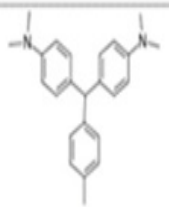
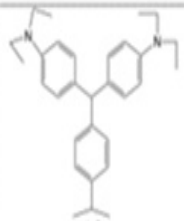
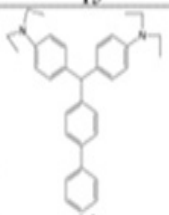
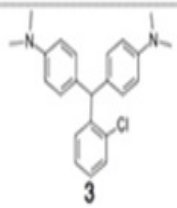
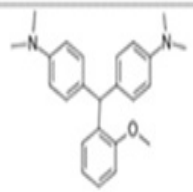
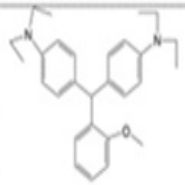
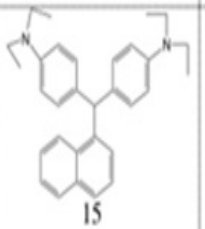
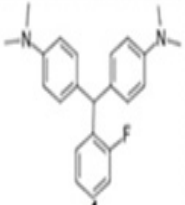
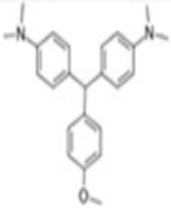
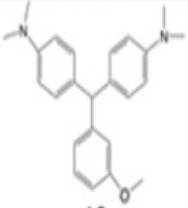
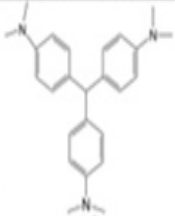
|  1 | 100 |  5 | 350 |  9 | 430 |  13 | 110 |
|  2 | 450 |  6 | 275 |  10 | 280 |  14 | 90 |
|  3 | 340 |  7 | 200 |  11 | 325 |  15 | 280 |
|  4 | 60 |  8 | 320 |  12 | 40 |  16 | 600 |

The initial radiolytic reaction is the dissociation of the radical initiator and subsequent reaction of the resultant halocarbon radical with the DTB. Initially a triarylmethane radical intermediate forms which can be transiently detected at 425nm. Then the colored dye cation forms, absorbing at 600 to 640nm depending on the nature of the DTB.[14–16] An initial example of the color change of a prototype dosimeter formulated with a DTB and radical initiator in polyurethane is shown (Figure 2).

The density of the radical resides primarily on the methine carbon with some charge distribution to the to the nitrogen substituents.[16–18] Radical stability is perhaps largely due to steric protection[16] of the methine carbon, which is consistent with the observed radiation dose sensitivities of the halogenated DTBs (Table 1). These varied from 3.4 times greater than LMG, for the most sterically hindered bromide derivative 2, 0.6 times that of LMG for the ortho-fluoride 4 This is also consistent for the ortho-methyl derivative 5 being more dose sensitive than para-methyl derivative 6. There are electronic contributions of the para-methyl 6 in stabilizing the radical relative to 1 which has no para substituent. For the ortho- and para-methoxy derivatives, 7 and 8, respectively, the interpretation of the steric and electronic contributions is not as straight forward since 8 is more dose sensitive

**Citation:** Adamovics JA. Three dimensional radiochromic detection of therapeutic radiation. *MOJ Biorg Org Chem.* 2018;2(2):88–91.
DOI: 10.15406/mojboc.2018.02.00061

than 7 and almost that of 5 while 12 with a Meta methoxy substituent is the least dose sensitive of the DTBs tested. In general the N,N diethyl substituents are more dose sensitive than the N,N dimethyl DTBs (5 vs 9) which may be rationalized by additional greater hinderance of the central carbon or increase in the nitrogen basicity. Overall, the most dose sensitive was 16 which has an additional N,N dimethyl substituent.

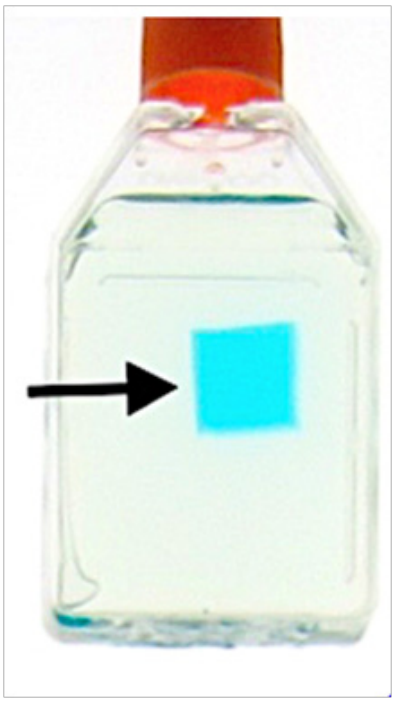


**Figure 2** Square field irradiation of LMG in polyurethane.

Another important characteristic is the post-irradiation color stability where in general the greatest steric hinderance provides the greatest color stability. All of the para substituted DTBs studied have demonstrated increased color fading over time compared to the ortho substituted derivatives.

### Dosimeters

Due to the versatile nature of the dosimeter system described above virtually any shaped dosimeter can be fabricated as shown in Figure 3.

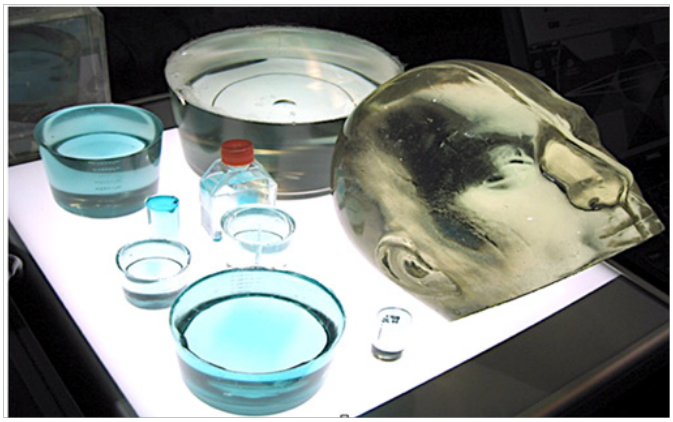


**Figure 3** 3D dosimeters for a variety of radiation therapies.

## Overview

The flexibility of formulation of the DTBs and polyurethane has allowed a wide range of clinically related applications to be addressed. Examples include variation of the dosimeter dose sensitivity to match the radiation treatment requirements, internally delivered radiation in which dosimeters were created with a cavity to hold radioactive seeds, Preparation of deformable dosimeters with the same elastic properties as human tissue and reusable dosimeters which may be irradiated, measured, bleached, and irradiated again.[12,17] Recently, advances in 3D dosimetry have made possible the study of alternative treatment approaches such as the addition of nanoparticles containing metals to the dosimeter to evaluate enhanced radiation effects[18] and the use of rodent-morphic dosimeters in evaluating radiation treatment plans.[19]

## Acknowledgements

Author contributed toward data analysis, drafting and revising the paper and agrees to be accountable for all aspects of the work.

## Conflict of interest

There is no conflict of interest.

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**Citation:** Adamovics JA. Three dimensional radiochromic detection of therapeutic radiation. *MOJ Biorg Org Chem.* 2018;2(2):88–91.
DOI: 10.15406/mojboc.2018.02.00061