Chemical dosimeters

John A Adamovics and Robert J Coakley
Department of Chemistry, Biochemistry and Physics, Rider University
2083 Lawrenceville Road, Lawrenceville, NJ 08648-3099, USA
E-mail : jadamovics@rider.edu

Abstract. Measuring radiation exposure has long been a priority in radiation therapy. Over the last 115 years numerous chemical-based dosimeters have been developed to measure radiation exposure. These dosimeters contain either metal complexes or leuco dyes. Among the factors which influence dose sensitivity and color stability in leuco dye based dosimeters are chemical structure and the solvent content in the formulation.

1. Introduction
Since the early 1900s color changes have been utilized as a means of quantitatively measuring radiation. Chemical-based radiochromic dosimeters utilize either metal complexes or leuco dyes.

2. Metal Complexes
One of the first popular dosimeters was developed by Sabouraud and Noire in 1904 [1]. This dosimeter employed a small disk (pastille) of barium platinocyanide, which after irradiation changes from a green to a dark yellow-orange. These dosimeters were widely utilized until the 1930s. More recently, a ferrous hexacyanide variant (also known as Turnbull dye or Prussian Blue) was evaluated as a 3D gel dosimeter with a maximum wavelength absorbance of 690 nm (Figure 1). [2].

![Figure 1. Structure of barium platinocyanide (left) and ferrous hexacyanide (right).](image)

By 1927 Fricke and Morse developed a radiochromic dosimeter incorporating a ferrous sulfate solution (Fricke solution). Upon irradiation, ferrous (Fe²⁺) ions are oxidized to ferric ions (Fe³⁺) [3]. During irradiation water is decomposed to reactive HO⁻ and H⁻ radicals which further react with oxygen to...
produce the hydroperoxy radical. This oxidizes the ferrous ions (Scheme 1). Other metals such as ceric sulfate have also been used in an aqueous dosimeter [4].

In order to stabilize the geometric dose information in the Fricke dosimeter, aqueous based gel matrices containing the chelator xylenol orange (XO) are used [5]. When analyzed spectrophotometrically, a non-irradiated ferrous/agarose/ XO gel shows visible-light absorption at 440 nm; after exposure to ionizing radiation, the maximum absorption shifts to 585 nm.

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\text{H}^+ + \text{O}_2 \rightarrow \text{HO}_2^-
$$

$$\text{HO}_2^- + \text{Fe}^{2+} \rightarrow \text{HO}^- + \text{Fe}^{3+}
$$

$$\text{HO}^- + \text{H}^+ \rightarrow \text{H}_2\text{O}_2
$$

$$\text{HO}^- + \text{Fe}^{2+} \rightarrow \text{HO}^- + \text{Fe}^{3+}
$$

$$\text{H}_2\text{O}_2 + \text{Fe}^{2+} \rightarrow \text{HO}^- + \text{Fe}^{3+} + \text{HO}^-
$$

**Scheme 1.** Ionizing radiation reactions in the Fricke dosimeter.

Seventeen different chelators have been studied as potential alternatives to XO with methyl thymol blue being a potential alternative [6] (Fig 2). Since 1927, over 5,500 dosimeter references to ferrous sulfate dosimetry have been reported [7].

3. Leuco Dyes

Leuco color formers undergo a switch between two chemical forms, one of which is colorless. This transformation occurs by the input of energy either from heat, light, ionizing radiation or change in pH. This redox process is reversible [8]. There are at least 7 leuco dye structural families each with distinctive structures [8].

3.1 Tetrazolium

One group is tetrazolium salt derivatives, which have been increasingly employed in both 3D dosimeters [9-12] and 2D films [13] over the past two years.

**Scheme 2.** Reduction of a colorless tetrazolium salt to a colored Formosan.
3.2. Triarylmethanes (TAM)

TAM leuco dyes, formulated primarily in organic solvents, have been thoroughly studied [14]. In the early 1950s the US Army issued glass vials filled with bromocresol purple (a pH indicator) dissolved in chloroform to determine possible radiation exposure from a nuclear explosion [15]. TAMs have also been incorporated into polyvinyl chloride and other polymer matrices for high dose 2D film for non-clinical dosimeter applications [16] and more recently in polyurethane sheets for 2D clinical applications [17].

For the last 14 years, we have utilized TAMs as color formers (1-2%) in a clear polyurethane matrix containing 0.5% radical initiator, with the remainder organic solvents that are used to solubilize the TAM and initiator [18]. We focused primarily on leuco malachite green (LMG, Scheme 3, and #1, Table 1) derivatives, a N,N,N',N'-tetramethyl triarylmethane (DTM) which we synthesized [18], and secondarily on leuco crystal violet (LCV, #16, Table 1). In order for the TAM based dosimeter to be sufficiently reactive to a clinical radiation dose, a radical initiator is required. The most effective class of initiators are halocarbons [23, 24]. The dose sensitivity was found to be consistent with the bond energy of the carbon-halogen bond. The observed sensitivity was in the order R3C-I > R3C-Br > R3C-Cl [24].

The first step upon irradiation is the homolytic cleavage of the carbon-halogen bond, creating a halo radical which subsequently abstracts the methine proton, providing a planar carbocation which absorbs at 633 nm.

![Scheme 3. Mechanism of TAM oxidation by ionizing radiation.](image-url)
The relative optical response of sixteen TAMs is tabulated in Table 1. The TAM molecular structure has significant impact on the dose sensitivity. After irradiation, the methine radical (Scheme 3) is delocalized over the entire triarylmethane [25]. Radical stability is largely due to steric protection [25] of the central carbon, which is consistent with what is observed for the radiation dose sensitivity of the TAMs. The sensitivity varied from 3-4 times greater than LMG for the most hindered bromide derivative 2 to 0.6 less dose sensitivity than LMG for ortho-fluoro derivative 4 (Table 1). This is also consistent for the ortho-methyl derivative 5 being more dose sensitive than the 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, the interpretation of the steric and electronic contributions is not as straightforward since 8 is more dose sensitive than 7 and almost that of 5 while in 12 the meta substituent is the least dose sensitive of the DTM tested. In general the N,N-diethyl substituents are more dose sensitive than the N,N-dimethyl DTMs (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 but is not sterically hindered.

Another critical dosimeter characteristic is post irradiation stability. In general, the more hindered TAMs are more stable post irradiation but that is also influenced by the amount of solvent in the formulation. The hindered TAM, 2,4 dimethyl-LMG (Structure 13, Table 1) shows a stable radiochromic response over 500 hours with 4% solvent in the formulation, while the color is totally bleached after 320 hours when formulated with 15% solvent. The mechanism is not clear.

![Figure 3](image.png)

**Figure 3.** Post irradiation stability of 2,4 dimethyl LMG at 4%, 7% and 15% solvent content.

There has been a long-term interest in TAMs containing cyanide where the methine H is replaced by cyanide which makes the bond at the central atom more labile [26, 27] but to date only 2D dosimeter films have been developed. This is also true of the most common 2D Gafchromic film which is based on the polymerization of diacetylenes.
4. Conclusions
This review is intended to provide the reader with a comprehensive set of references from the two major categories of chemical-based dosimeters - metal complexes and leuco dyes and an update on what is understood of the mechanism of reaction.

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