Enhanced method for determining the low-LET saturation dose of PRESAGE®

Simon J Doran¹, Paolo Pellicioli¹, John Adamovics³ and Elke Brauer-Krisch²
1CRUK Cancer Imaging Centre, Institute of Cancer Research, London, UK
2European Synchrotron Radiation Facility, Grenoble, France
3Department of Chemistry and Biology, Rider University, Lawrenceville, NJ, USA

E-mail: Simon.Doran@icr.ac.uk

Abstract. An accurate value for the saturation dose of PRESAGE® is important in elucidating the mechanism of the so-called quenching phenomenon in the 3-D dosimetry of proton beams. This quantity is difficult to obtain, because it involves measuring the optical density of a set of very highly attenuating samples. We present a novel method that makes use of the ability to irradiate microscopically-thin “slices” of a cuvette using microplanar beams from a synchrotron. Using the new method, we were able to measure optical densities of up to 50 cm⁻¹ using a standard spectrophotometer, and we derived a value 14000 Gy for the saturation parameter $D_{37}$.

1. Introduction

Quenching of dosimeter response is a major issue in the measurement of the radiation dose from proton and other ion beams. “Quenching” is said to occur when, for a given physical dose, the dosimeter gives a lower output reading for radiation with high linear energy transfer (LET) than for the same dose of low-LET radiation. In the case of 3-D chemical dosimeters, that output reading might be the $R_2$ value (polymer gel, read out with MRI [1]) or optical density (Fricke gel [2] or PRESAGE® [3] read out with optical-CT). Although it has been reported that some formulations of polymer gel do not exhibit quenching [4], most chemical dosimeters (and many “physical” dosimeters, too) are affected to some degree or other. The effects are particularly noticeable for measurements made at the Bragg peak in proton treatments and the implications of this for accurate dosimetry have been explored in [5].

The precise origin of the under-response in 3-D dosimeters still remains to be elucidated. Gustavsson et al [1] hypothesised that the effect was attributable to increased recombination of the free-radicals produced by the irradiation, before they could effect a chemical change in the dosimeter. A second possibility is local saturation of the dosimeter along the tracks of the protons or ions, where a very high dose is localised within a microscopic region. The latter situation may be described using the formalism of track structure theory [6]. A key parameter in this analysis is the dose required to saturate the dosimeter response at low LET. It can be shown that the expected dose-response relation is a single-exponential recovery curve of form $OD \propto 1 - \exp(-D/D_{37})$, where $D_{37}$ is the dose required to convert a fraction $1/e$ (37%) of the active elements in the dosimeter. We have previously made several attempts to determine the value of $D_{37}$ using a spectrophotometer and optical CT scanner [7, 8].
The significant experimental difficulty in measuring this parameter is illustrated in figure 1. Irradiated PRESAGE® cuvettes are typically analysed using a spectrophotometer, but all such instruments have a finite dynamic range: the minimum signal detectable above the noise threshold determines the maximum optical density that can be measured. On our current spectrophotometer (Cary 50, Agilent Technologies, Santa Clara, CA), this value is a little less than 3 cm$^{-1}$. As can be seen from the spectra in figure 1a, readings for the samples with the lowest four doses are continuous across the whole spectral range, but as the dose is increased further, severe distortions of the spectra occur in the region corresponding to the dose-dependent part of the PRESAGE® absorption and, consequently, the values in the graph of figure 1(b) are incorrect. Notice that the actual signal reaching the detector decreases exponentially with increasing optical density and so 1 cm cuvette samples that are highly irradiated pass virtually no light.

Our previous work [8] overcame this problem partially by employing a special type of cuvette with 2 mm path length. However, this proved unsuitable for formulation of PRESAGE® studied here, which had an extremely high saturation dose, resulting in very large optical densities. Hence, a new method was devised in which only a portion of each cuvette was irradiated, as described below. Because the ultra-high absorption can be confined to just a thin “slice” of the sample, the overall attenuation remains a level that can be measured. A knowledge of the geometry of the situation allows us to back-calculate what the attenuation would have been had the whole sample been irradiated.

2. Material and Methods
All measurements were performed on cuvettes with a 1 cm optical path length, filled with PRESAGE® (Heuris Pharma, Skillman, NJ). Samples were irradiated on beamline ID-17 at the European Synchrotron Radiation Facility (ESRF) and a full description of the general irradiation methodology and beamline characteristics has been given in previous publications, e.g., [9]. Cuvettes were placed immediately distal to a number of Perspex sheets to ensure appropriate electron equilibrium and such that the centre of the cuvette was located at the standard reference depth used in rest of the local dosimetry programme.

Figure 1. (a) Typical set of spectra obtained from spectrophotometer, illustrating the problems of a limited dynamic range in output optical density; (b) optical density values at peak of PRESAGE® spectrum (638 nm).
Three separate sets of irradiations were performed: (i) Low-dose range: 7 samples were irradiated with a field size of 15 mm × 30 mm, thus covering the complete width of the cuvettes. The calculated doses at the reference point were 20, 30, 50, 100, 130, 160 and 200 Gy. (ii) Mid-dose range: 9 samples were irradiated with a “slit pattern” of 2 mm width (see [10]) to doses of 160, 200, 300, 500, 750, 1000, 1300, 1600 and 2000 Gy. (iii) High-dose range: 9 samples were irradiated with a microplanar beam of width 100 µm to doses of 1600, 2000, 3000, 5000, 7500, 10000, 12500, 15000 and 20000 Gy.

Figure 2. Spectra and graph of spectral value at a single wavelength (680 nm) for the complete set of samples. Note the difference between the vertical scales on the left and right. On the left are the values of optical density measured by the spectrophotometer, assuming a uniform 1 cm cuvette. On the right are the values of optical density corrected for the path length through the high-dose region of the sample. We are unclear of the reason why the linearity of the top-right graph is so poor (the point at 100 Gy is an unexpected outlier) or for the behavior of the first three points on the middle right graph.)
3. Results and discussion
The new method uses two techniques to read samples of high optical density. Different ranges of absorption coefficient \( \alpha \) can be accommodated by irradiating different “slice thicknesses”, \( d \) out of a total cuvette thickness of \( d_0 \). Since the spectrophotometer measures the total attenuation \( A \propto \exp(-\alpha d) \exp(-\alpha_0 [d_0 - d]) \), it suffices to keep the product \( \alpha d \) within the measureable range, with \( \alpha_0 \), the absorption coefficient of unirradiated PRESAGE®, rapidly becoming trivial as the dose escalates. With prior knowledge of the dose-response relation, one could arrange for all spectra to be measured without the distortions illustrated in figure 2. However, since we did not “know the result in advance”, our choice of thicknesses was not optimal. The second trick is thus to measure at a wavelength slightly away from the absorption maximum and, after experimentation, we chose 680 nm. Figure 2 shows the complete set of data obtained in the three ranges, whilst figure 3 displays all the data on a single graph, with a fit to the model. The fit parameter obtained was \( D_{37} = 14000 \text{ Gy} \). Further analysis at a number of different wavelengths is needed to determine the most appropriate method for calculating the error estimate in this value. However, a preliminary point of interest to note is that this value is significantly in excess of the corresponding value obtained in our previous study [8], indicating that the PRESAGE® saturation dose is formulation-dependent.

4. Conclusion
With the new, enhanced method, it is possible to measure dose-response curves for 3-D dosimeters out to extremely high doses, thus simulating the “micro-dose” along a proton beam. In principle, if track structure theory is applicable and does indeed explain the quenching phenomenon, PRESAGE® formulations with higher values of \( D_{37} \) should exhibit reduced quenching.

5. References
[1] Gustavsson H et al 2004 Phys. Med. Biol. 49 3847-55
[2] Bäck S Å J et al 1999 Phys. Med. Biol. 44 1983
[3] Al-Nowais S et al 2009 Appl. Radiat. Isotop. 67 415-8
[4] Zeidan O et al 2010 Med. Phys. 37 2145-52
[5] Doran S et al 2015 Phys. Med. Biol. 60 709-26
[6] Waligorski M et al 1986 Int. J. Radiat. Appl. Instru. D. 11 309-19
[7] Al-Nowais S et al 2009 J. Phys.: Conf. Ser. 164 012043
[8] Nowais S A et al 2010 J. Phys.: Conf. Ser. 250 012034
[9] Doran S J et al 2010 Phys. Med. Biol. 55 1531-47
[10] Rahman A A et al 2011 Phys. Med. Biol. 56 4177