Formulation Studies

Customising PRESAGE® for diverse applications

T Juang, J Newton, M Niebanck, R Benning, J Adamovics and M Oldham
2013 J. Phys.: Conf. Ser. 444 012029

PRESAGE® is a solid radiochromic dosimeter consisting of a polyurethane matrix, a triarylmethane leuco dye, and a trihalomethane initiator. Varying the composition and/orrelative amounts of these constituents can affect the dose sensitivity, post-irradiation stability, and physical properties of the dosimeter. This allows customization of PRESAGE® to meet application-specific requirements, such as low sensitivity for high dose applications, stability for remote dosimetry, optical clearing for reusability, and tissue-like elasticity for deformable dosimetry. This study evaluates five hard, non-deformable PRESAGE® formulations and six deformable PRESAGE® formulations and characterizes them for dose sensitivity and stability. Results demonstrated sensitivities in the range of 0.0029 – 0.0467 ΔOD/(Gy·cm) for hard formulations and 0.0003 – 0.0056 ΔOD/(Gy·cm) for deformable formulations. Exceptional stability was seen in both standard and low sensitivity non-deformable formulations, with promising applications for remote dosimetry. Deformable formulations exhibited potential for reusability with strong post-irradiation optical clearing. Tensile compression testing of the deformable formulations showed elastic response consistent with soft tissues, with further testing required for direct comparison. These results demonstrate that PRESAGE® dosimeters have the flexibility to be adapted for a wide spectrum of clinical applications.

An investigation into ultra-sensitive substituted leucomalachite dye derivatives for use in the PRESAGE® dosimeter

M Alqathami, J Adamovics, R Benning and A Blencowe
2013 J. Phys.: Conf. Ser. 444 012034

A comparison between a commercial leucomalachite green (LMG) dye and three newly synthesised derivatives incorporated into the PRESAGE® dosimeter was carried out to determine their effect on the sensitivity and post-response photofading of the dosimeter. For all of the substituted LMG derivatives (with either methoxy, chlorine or bromine substituents), the sensitivity of the resulting dosimeters to radiation dose increased significantly and was dependent on the type of LMG derivative used, with the bromine substituted derivative showing the highest sensitivity increase (450%) followed by chlorine and methoxy substituted derivatives (340%, 200 %, respectively) relative to commercial LMG. All LMG dyes investigated showed similar post-response photofading characteristics except the methoxy-LMG derivative, which showed a slight improvement in post-response photo-retention.

Evaluation of ultra-sensitive leucomalachite dye derivatives for use in the PRESAGE dosimeter

Alqathami, Mamdooh; Adamovics, John; Benning, Ron; Qiao, Greg; Geso, Moshi; Blencowe, Anton

Radiation Physics and Chemistry, **Radiat Phys Chem**. 2012;91

In this study we carry out a comparison between the com. available leucomalachite green (LMG) dye and three newly synthesized derivs. (with either methoxy, chloro or bromo substituents) incorporated into the PRESAGE dosimeter to det. their effect on the sensitivity and post-response photostability of the dosimeter. In addn., the influence of the new LMG derivs. on the basic radiol. properties of the PRESAGE dosimeter was also investigated. The dosimeters were prepd. in spectrophotometric cuvettes, irradiated with a 6 MV X-ray beam, and the change in optical density of each dosimeter was measured.

Optimizing the sensitivity and radiological properties of the PRESAGE dosimeter using metal compounds

Alqathami, Mamdooh; Blencowe, Anton; Qiao, Greg; Adamovics, John; Geso, Moshi

Radiation Physics and Chemistry (2012), 81(11), 1688-1695.

The aim of this study is to investigate the radiation-modifying effects of incorporating com. available bismuth-, tin- and zinc-based compds. in the compn. of the PRESAGE dosimeter, and the feasibility of employing such compds. for radiation dose enhancement. Furthermore, we demonstrate that metal compds. can be included in the formulation to yield water-equiv. PRESAGE dosimeters with enhanced dose response. Various concns. of the metal compds. were added to a newly developed PRESAGE formulation and the resulting dosimeters were irradiated with 100 kV and 6 MV photon beams.

Optimization of the sensitivity and stability of the PRESAGE dosimeter using trihalomethane radical initiators

Mamdooh, A Alqathami, A Blencowe, G Qiao, D Butler, and M Geso

Radiation Physics and Chemistry 81:867-873 (2012)

The aim of this study is to investigate the effect of trihalomethane radical initiators on the radiological properties,radiation dose sensitivity and postresponse photo-stability of the PRESAGE dosimeter. Different PRESAGE dosimeters containing 50 and100 mM of iodoform(CHI3), bromoform(CHBr3) or chloroform(CHCl3) radical initiators where fabricated and irradiated with 6MVphotons for a range of radiation doses from 0 to 30Gy. A comparison between sensitivity and radiological properties of the PRESAGE dosimeters with the different radical initiators was carried out.Optical density changes of the dosimeters before and after irradiation were measured using

aspectrophotometer. The incorporation of different radical initiators in the composition of the PRESAGE dosimeter resulted in variation of the radiation dose sensitivity and radiological properties of the dosimeters depending on the type and concentration of the radical initiator used,with iodoform showing the highest dose-response slope followed
by bromoform and chloroform. However, at100mM iodoform, the effective atomic number was significantly higher than water (Zeff16). This enhancement in dose-response was found to be directly related to the carbon–halogen bond dissociation energy and to the radiological properties of each individual radical initiator used in this study. Furthermore,the post-response stability of the PRESAGE dosimeters over two weeks remained stable regardless of the trihalomethane radical initiator employed,with negligible change in the post-response stability and linearity of the PRESAGE dosimeters.

Novel multicompartment 3-dimensional radiochromic radiation dosimeters for nanoparticle-enhanced radiation therapy dosimetry

Alqathami Mamdooh; Blencowe Anton; Yeo Un Jin; Doran Simon J; Qiao Greg; Geso Moshi
International journal of radiation oncology, biology, physics
(2012), 84(4), e549-55.
PURPOSE: Gold nanoparticles (AuNps), because of their high atomic number (Z), have been demonstrated to absorb low-energy X-rays preferentially, compared with tissue, and may be used to achieve localized radiation dose enhancement in tumors. The purpose of this study is to introduce the first example of a novel multicompartment radiochromic radiation dosimeter and to demonstrate its applicability for 3-dimensional (3D) dosimetry of nanoparticle-enhanced radiation therapy. METHODS AND MATERIALS: A novel multicompartment phantom radiochromic dosimeter was developed.

Development and characterization of a novel PRESAGE formulation for radiotherapy applications
Mostaar, A.; Hashemi, B.; Zahmatkesh, M. H.; Aghamiri, S. M. R.; Mahdavi, S. R.
Applied Radiation and Isotopes (2011), 69(10), 1540-1545. I
A novel water equiv. formulation of PRESAGE dosimeter more suitable for radiotherapy applications has been introduced and its radiol. water equivalency has been investigated. Furthermore, its radiol. properties have been compared with an existing PRESAGE formulation over an energy range from 10 to 20 MeV. Monte Carlo simulation method has been implemented to det. and compare depth dose profiles in both of the PRESAGE formulations at two different photon energies (140 KV_P and 6 MV). The results show that our proposed PRESAGE formulation is more water equiv. than its known formulation

A basic dosimetric study of PRESAGE: the effect of different amounts of fabricating components on the sensitivity and stability of the dosimeter
A Mostaar, B Hashemi, M H Zahmatkesh, S M R Aghamiri and S R Mahdavi
Phy Med and Biol 55; 903-912 (2010)
Over the past few years there has been much interest in the development of three-dimensional dosimeters to determine the complex absorbed dose distribution in modern radiotherapy techniques such as IMRT and IGRT. In routine methods used for three-dimensional dosimetry, polymer gels are commonly used. Recently, a novel transparent polymer dosimeter, known as PRESAGE, has been introduced in which a radiochromic color change is observed upon radiation. PRESAGE has some advantages over usual polymer gel dosimeters. It has been noted that the sensitivity of PRESAGE can be changed when different amounts of the components are used for its fabrication. This study has focused on the assessment of dosimetric characteristics of PRESAGE for various amounts of components in its formulation. To achieve this, RESAGE dosimeters were fabricated using various amounts of their constituting components. Then the dosimeters were irradiated to 60Co gamma photons for a range of radiation doses from 0 to 50 Gy. Consequently, the light absorption changes of the dosimeters were measured by a spectrophotometer at different post-irradiation time periods. It was generally observed that as the concentration of the radical initiator is increased, the PRESAGE dosimeter sensitivity is increased while its stability is decreased. Furthermore, it was noted that with the high concentration of the radical initiator and leuco dye, the sensitivity of PRESAGE is decreased.

Three-dimensional shaped solid dosimeter and method of use
By Adamovics, John A.
U.S. Pat. Appl. Publ. (2007), US 20070020793 A1 20070125
The invention relates to a solid plastic three-dimensional dosimeter which is useful in treatment planning, optimization of the radiation field, dose verification, dose validation, commissioning, and quality assurance of complex radiotherapy procedures. Dosimeters of the invention can be formed in any clin. relevant shape, and contain a reporter leuco dye which forms a colored image upon irradn.

PRESAGE - Development and optimization studies of a 3D radiochromic plastic dosimeter - Part 1
Adamovics, J.; Jordan, K.; Dietrich, J.
Journal of Physics: Conference Series (2006), 56, 172-175.
The polymn. of 6 different transparent plastics as potential 3-dimensional dosimeter matrixes was studied. 6 Different leuco dyes and 16 different free radical initiators were evaluated and the photoreactivity of the dosimeter was

studied so that the effect of exposure to UV could be minimized. A polyurethane matrix with 2% LMG leuco dye contg. a C halogen initiator is sensitive to high energy radiation and has a linear response to dose. However, this potential 3-dimensional dosimeter must be protected from UV and blue light.

PRESAGE - Development and optimization studies of a 3D radiochromic plastic dosimeter - Part 2

By Adamovics, J.; Guo, P.; Burgess, D.; Manzoor, A.; Oldham, M.
Journal of Physics: Conference Series (2006), 56, 176-178
In a previous study, 7 different transparent plastics were evaluated as dosimeter matrixes along with 6 different leuco dyes as the radiochromic agent. Polyurethane along with the triphenylmethane, leucomalachite green, are the optimal combination of the formulation variables studied. The dosimeter sensitivity and post irradn. stability of an addnl. plastic matrix and 5 different leuco dyes were examd. Two formulations exhibit the most future promise for practical use in 3-dimensional dosimetry with respect to their initial sensitivity and stability.

A new approach to radiochromic three-dimensional dosimetry-polyurethane

By Adamovics, J.; Maryanski, M. J.
From **Journal of Physics: Conference Series** (2004), 3, 172-175
Three-dimensional dosimeter material was produced from a diisocyanate and a polyol to form a polyurethane matrix that contained radiochromic dyes in the leuco-form and free radical initiators. The dyes could be tri-Ph methanes, spiropyrans, chromenes, oxazines, phenazines, phthalides, fluoranes, tetrazoles, and polydiacetylenes. Org. peroxides, halocarbons, azo, carbonyland sulfur compds. could act as free radical initiator. Irradn. induced free radicals that oxidized the leuco-dye, and after radiolytic oxidn. the dye exhibited absorbance in the visible range.

Enhanced Performance of PRESAGE - Sensitivity, and Post- Irradiation Stability

J Adamovics, J Dietrich, K Jordan
Med. Phys. 32, 2004 (2005); SU-FF-T-239
Purpose: To improve the dose sensitivity and to control the post-irradiation radiochromic response of
PRESAGE™ a 3D dosimeter. Method and Materials: One cm plastic cuvettes were filled with formulations of PRESAGE™ that varied in the composition of leuco malachite green(LMG), a radical activator and a
dissolution solvent. The dosimeters were irradiated using a Varian 600C linear accelarator with a 4 MV photon beam. The dosimeters were irradiated at doses ranging from 10cGy to 60Gy (250 cGy/min) and measured on a Hitachi-Perkin Elmer 204 spectrometer at 630 nm. The absorbances were measured 10 minutes after irradiation and up to a week post-irradiation. The sensitivity of

PRESAGE™ to room light was investigated by placing dosimeters in a laboratory under constant room light at 22°C for approximately 6 hr and periodically measuring the radiochromic response. Results: The radiochromic response at 630 nm was linear from 0 to approximately 30 Gy with a slope of 0.16 OD/Gy and with an error, R2, of 0.9995. The lower limit of dose measurement of the dosimeter is 10cGy. The stability of the post-irradiation radiochromic response can be varied with minor detectable radiochromic response loss after 7 days (<1%/24 hr) to nearly 100% loss of radiochromic response 24 hr. When exposed to room light the photochromic background increases 0.05 cm-1/ hr. Conclusion: The performance characteristics of PRESAGE™ have been enhanced by increasing the sensitivity of the dosimeter. The rate of thermal bleaching post-irradiation can be controlled by varying the ratios of the LMG to the radical activator and quantity of dissolution solvent. The ability to control the rate of losing the radiochromic dose distribution is an important characteristic for a potentially reusable dosimeter. Precautions must be taken to minimize the exposure of PRESAGE™ to room light.

Other Studies Plasma Protein-Binding, Ionization Constant. Effect of Compatible Excipients on dissolution, Kinetic Studies of Solution Degradation, Use of Radio-labeled Drug. Physicochemical parameters: 2. Organoleptic propertiesÂ Odor may be pungent, sulfurous, fruity, aromatic and odorless. Taste may be acidic, bitter, bland, intense, sweet and tasteless. Bulk characterization studies: It is needed to identify all the solid forms that may exist as a consequence of the synthetic stage such as the presence of polymorphs. A Review on Pharmaceutical Preformulation Studies in Formulation and Development of New Drug Molecules. International Journal of Pharmaceutical Science and research, 7(6): 2313-2320. Kulkarni, S., Sharma, S. and Agrawal, A. (2015). Preformulation â€“ A Foundation For Formulation Development.Â Gibson, M. (2004). Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form. Florida: CRC Press LLC. Onyishi, I. V. (2015). Study of these parameters and suitable molecular modification can be linked to generation of effective, safer, stable, and reliable pharmaceutical formulation. Therefore, preformulation study is an approach for generation of pharmaceutical formulation which utilizes knowledge and area application of toxicology, biochemistry, medicinal chemistry, and analytical chemistry. The highlighted chapter is framed with a vision to provide an in-depth knowledge about pharmaceutical formulation development.