Opportunities for improving the performance of LCV micelle gel dosimeters: II. Recipe optimization

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Abstract. Designed experiments and empirical models are used to optimize a Leuco Crystal Violet (LCV) micelle gel recipe to improve dose sensitivity and initial colour. The optimized recipe contains 0.75 mM LCV, 17.0 mM Cetyl Trimethyl Ammonium Bromide (CTAB), 120 mM 2,2,2-trichloroethanol (TCE), 25.0 mM tri-chloro acetic acid (TCAA), 4 wt% gelatin and ~96 wt% water. Dose sensitivity of the optimized gel is 1.5 times higher than Jordan's standard LCV gel. Spatial integrity of the 3D dose distribution information in 1L jar phantoms made using this recipe is maintained for more than two weeks.

1. Introduction

LCV micelle gel dosimeters can be read out using optical scanners and have the potential to produce accurate 3D dosimetry [1] results with excellent spatial stability [2-4]. Babic *et al.* [3] recommended a gel recipe containing 4.0 wt% gelatin, 4.0 mM triton x-100 (Tx100) surfactant, 25.0 mM TCAA, 1.0 mM LCV, and ~ 96.0 wt% water. This recipe is referred to as Jordan's standard LCV gel throughout this article. In our previous work, effects of components in LCV micelle gel were investigated [5]. We found that dose sensitivity increases with increasing Tx100 but, unfortunately, initial colour of the un-irradiated gels also increases. When Tx100 was replaced with CTAB, colourless gel was produced, but dose sensitivity decreased. TCE and other chlorinated compounds were tested as sensitizers for LCV micelle gels and TCE was chosen for further study because it was the most effective for improving sensitivity. Additional testing and optimization of the recipe are conducted in the current work.

Design of Experiments (DOE) techniques [6-7] involve applying formal statistical methods for planning and conducting experiments and for extracting, analyzing and interpreting data to draw conclusions and build models that can be used for optimization. DOE uses an efficient set of experimental runs to investigate the effects of the critical factors (inputs) on the responses (outputs) of interest. Rather than studying the influence of one input at a time, experiments are designed so that multiple factors are varied together, providing information about interactions between variables. In two-level full-factorial designs (a widely used DOE technique), each input variable is set at two different levels: low (coded as -1) and high (coded as 1). A two-level full factorial design with k factors is called a 2^k design, because 2^k experimental runs are required to examine all possible combinations of low and high values for the k factors (see Fig.1). Replicate points are often added at the centre of a 2^k design to estimate typical experimental error encountered in the experiment [6-7]. In the current paper, a 2^3 factorial experiment corresponding to figure 1 is conducted and linear

regression models are developed to predict initial colour (absorbance at 590 nm) and dose sensitivity. This information is used to guide additional experimentation and to develop an optimized gel recipe

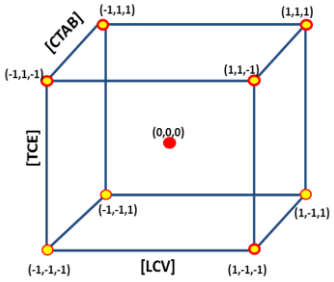

Figure 1. Two-level three-factor (2^3) full factorial design with central point. The three factors here are concentrations of LCV, TCE, and CTAB. Note that the low and high levels of the factors are shown in coded form.

2. Materials and Methods

2.1. Gel preparation, irradiation, and scanning

The following manufacturing procedure was followed to manufacture gels:

1- Add gelatin (Type A, 300 Bloom porcine skin) to 75 wt% of the total deionized water in the recipe and let swell for 20 minutes. Stir while heating to 45 ^{o}C until gelatin dissolves.
2- Add CTAB, TCE and TCAA to the remaining 25 wt% of the deionized water and stir at room temperature for 10 minutes.
3- Add LCV to the mixture from step 2 and stir at room temperature for 5 minutes.
4- Pour LCV mixture from step 3 (at room temperature) into gelatin mixture from step 1 (at 45 ^{o}C) and stir for 2 minutes.

Samples of the final mixture, produced using a variety of recipes, were poured into 4.5 ml polystyrene cuvettes with 10 mm light path and sealed using a cap and Parafilm. pH was measured using a pH electrode. All gels were refrigerated at 4 ^{o}C for ~24 h and placed in a water bath at 22 ^{o}C for 20 minutes before irradiation. A few samples were poured into 23×85 mm clear glass cylindrical vials and photographed. A Varian Clinac 6EX linear accelerator was used to irradiate cuvettes to doses of 0, 5, 10, 15, 20, and 40 Gy at a dose rate of 400 cGy min^{-1}. Absorption spectra were measured ~20 minutes after irradiation using a SpectroVis Plus spectrophotometer between 380 and 900 nm. Absorbance measurements were calibrated using a reference cuvette containing deionized water [8].

2.2. Designed experiments to optimize LCV micelle gels made with CTAB and TCE

Results from the full factorial design with five replicates at the central point (runs 1-13 in table 1, conducted in random order) were used to fit linear regression models with dose sensitivity and initial colour as response variables [8]. Runs (14-17) were conducted to extend the range and complexity of the models. Optimization calculations to find the best recipe were performed using Excel.

2.3. Preliminary experiments in large-jar phantoms

Two 1 L polyethylene terephthalate jars were filled with gel using the optimized gel recipe (gel 19). These replicate phantoms were irradiated using a Varian Trilogy linear accelerator with RapidArc to test their response to spatially non-uniform radiation. One gel was irradiated with a single arc VMAT test treatment plan up to a maximum dose of 1795.3 cGy in the gel. The second gel was used for calibration and was irradiated with a 1850 MU, 12 MeV 6 x 6 cm^2 field electron beam (SSD=100 cm) delivered to the top surface of the gel (jar lid removed). The phantoms were imaged using a Vista Optical CT scanner under 590 nm LED illumination. Reference scan images were taken of each gel before irradiation. After irradiation, data scan images were also taken. Each gel was carefully timed to ensure that post-irradiation imaging times were consistent. To convert optical density values to dose, central-axis depth-dose data were obtained from the gel and compared to Wellhofer ionization-chamber water-tank measurements. This calibration was applied to the VMAT plan gel irradiation.

Table 1. Influence of CTAB, LCV and TCE on initial colour and dose sensitivity of LCV micelle gels. Concentrations of gelatin and TCAA were fixed at 4.0 wt% and 25.0 mM, respectively. Absorbance values were measured at 590 nm.

#	CTAB [mM]	LCV [mM]	TCE [mM]	Turbidity	Initial Colour	Initial Absorbance	Dose Sensitivity [$Gy^{-1}.cm^{-1}$]	pH
1	9.0	0.75	40.0	Clear	No	0.026	$7.46 \cdot 10^{-3}$	3.32
2	9.0	0.75	80.0	Clear	No	0.026	$9.10 \cdot 10^{-3}$	3.31
3	9.0	1.25	40.0	Clear	No	0.025	$6.59 \cdot 10^{-3}$	3.29
4	9.0	1.25	80.0	Clear	No	0.025	$9.44 \cdot 10^{-3}$	3.32
5	25.0	0.75	40.0	Clear	No	0.028	$8.59 \cdot 10^{-3}$	3.30
6	25.0	0.75	80.0	Clear	No	0.028	$9.86 \cdot 10^{-3}$	3.29
7	25.0	1.25	40.0	Clear	No	0.029	$9.37 \cdot 10^{-3}$	3.29
8	25.0	1.25	80.0	Clear	Light Blue	0.042	$1.15 \cdot 10^{-2}$	3.33
9	17.0	1.0	60.0	Clear	No	0.030	$9.17 \cdot 10^{-3}$	3.27
10	17.0	1.0	60.0	Clear	No	0.029	$1.00 \cdot 10^{-2}$	3.22
11	17.0	1.0	60.0	Clear	No	0.030	$9.60 \cdot 10^{-3}$	3.30
12	17.0	1.0	60.0	Clear	No	0.030	$9.37 \cdot 10^{-3}$	3.29
13	17.0	1.0	60.0	Clear	No	0.029	$1.00 \cdot 10^{-2}$	3.30
14	25.0	1.25	120.0	Clear	Light Blue	0.045	$1.28 \cdot 10^{-2}$	3.30
15	33.0	1.25	100.0	Clear	Light Blue	0.04	$1.19 \cdot 10^{-2}$	3.30
16	33.0	1.5	100.0	Turbid	---	0.207	----	3.31
17	33.0	1.25	120.0	Clear	Light Blue	0.05	$1.30 \cdot 10^{-2}$	3.31
18	15.5	0.75	80.0	Clear	No	0.028	$1.03 \cdot 10^{-2}$	3.34
19	17.0	0.75	120.0	Clear	No	0.031	$1.13 \cdot 10^{-2}$	3.31
20	33.0	1.25	120.0	Clear	Light Blue	0.048	$1.38 \cdot 10^{-2}$	3.31

3. Results and Discussion

Initial linear regression models (not shown) were fitted using runs 1 to 13 [8]. The model was used to select additional runs (14 to 17) that permit quadratic terms to be estimated. Gel 16 was cloudy (see figure 2) and was not used in the parameter estimation. The following model equations were obtained:

$$DS = \boldsymbol{a} + \boldsymbol{b}[\text{CTAB}] + c[\text{LCV}] + \boldsymbol{d}[\text{TCE}] + \boldsymbol{e}[\text{CTAB}][\text{LCV}] + f[\text{CTAB}][\text{TCE}] + g[\text{LCV}][\text{TCE}] + h[\text{CTAB}][\text{LCV}][\text{TCE}] + i[\text{CTAB}]^2 + j[\text{LCV}]^2 + k[\text{TCE}]^2 \quad (1)$$

$$A = \boldsymbol{l} + \boldsymbol{m}[\text{CTAB}] + \boldsymbol{n}[\text{LCV}] + o[\text{TCE}] + \boldsymbol{p}[\text{CTAB}][\text{LCV}] + q[\text{CTAB}][\text{TCE}] + r[\text{LCV}][\text{TCE}] + s[\text{CTAB}][\text{LCV}][\text{TCE}] + t[\text{CTAB}]^2 + u[\text{LCV}]^2 + v[\text{TCE}]^2 \quad (2)$$

where DS is dose sensitivity and A is initial absorbance at 590 nm. Statistically significant parameters are bolded and units are consistent with those in table 1 [8], where $\boldsymbol{a} = 5.39 \times 10^{-3}$, $\boldsymbol{b} = 2.13 \times 10^{-4}$, $\boldsymbol{d} = 3.16 \times 10^{-5}$, $\boldsymbol{e} = 1.16 \times 10^{-4}$, $\boldsymbol{l} = -6.04 \times 10^{-3}$, $\boldsymbol{m} = 1.23 \times 10^{-3}$, $\boldsymbol{n} = 2.32 \times 10^{-2}$, and $\boldsymbol{p} = -5.41 \times 10^{-3}$. Equations 1 and 2 were used to search for an optimized recipe using the objective function:

$$J = \omega DS - A \quad (3)$$

where ω is a weighting factor that controls the relative importance of achieving high dose sensitivity and low initial absorbance. Selecting a large value of ω causes the optimizer to select gel recipes with high dose sensitivity at the expense of darker initial colour; low values of ω result in selection of less-coloured gels at the expense of dose sensitivity. Bounds were enforced during optimization: 9 mM $\leq$ $[CTAB] \leq$ 33 mM, 0.75mM $\leq$ $[LCV] \leq$1.25 mM, 40 mM $\leq [TCE] \leq$ 120 mM to ensure that reasonable gel recipes would be selected. When ω= 3.362 Gy cm was selected so that the two terms in the objective function would have similar magnitudes, gel recipe 18 in table 1 was chosen when all parameters (significant and non-significant) in equations (1) and (2) were used in the models. The gel 19 recipe was selected when only significant parameters were used. When a higher value of ω= 33.62 Gy cm was selected so that dose sensitivity is more important to the optimizer than initial colour, gel

recipe 20 was chosen using all of the parameters and also using only the significant parameters. Gels 18 to 20 were prepared and irradiated. As expected, gel 20 had the highest dose sensitivity in the current study, but this gel was noticeably light blue in colour as shown in figure 2. Gel 19 had higher dose sensitivity (~1.5 times the sensitivity of Jordan's standard LCV gel) and was nearly colourless, making it promising for 3D gel dosimetry. As a result, gel 19 was selected for further testing in large jars. Dose measurements for the VMAT plan gel showed that dose distribution information is maintained over more than two weeks (figures 3b-d).

Figure 2. Photograph of un-irradiated vials containing gels manufactured at varying concentrations of CTAB, LCV, and TCE as described in table 1. Vial numbers 1 to 20 correspond to the sample numbers (1.1) to (1.20) in table 1. The vials were photographed in front of a page of text.

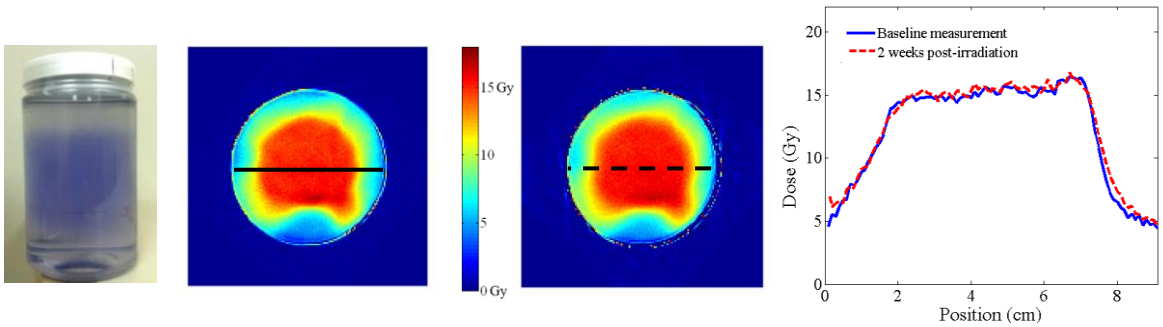

Figure 3. (a) Photograph of VMAT test treatment plan irradiation in a jar of LCV micelle gel. (b) Dose map of one slice of the gel dosimeter imaged 30 min. after irradiation. (c) Dose map of the same slice imaged 2 weeks after irradiation. (d) Cross-plane profiles of slices in (b) and (c).

4. Conclusions

Optimization of the recipe for LCV micelle gels made with CTAB and TCE was aided by a designed experiment. The resulting optimal gel containing 0.75 mM LCV, 17 mM CTAB, 120 mM TCE, 25.0 mM TCAA and 4 wt% gelatin, showed improved dose sensitivity (~1.5 times higher than Jordan's standard LCV gel) and low initial colour. Experiments in 1 L jars showed that spatial dose distribution information is maintained for > two weeks. Further testing is required to quantify the spatial and temporal stability and to test dose resolution and dose-rate behaviour.

5. References

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