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Optimization of Parameters for Polydiacetylenes Vesicles using Response Surface Methodology as a Function of Colorimetric Sensor

Syazwani Mohd Faizo[1,2], Naurah Mat Isa[2], Roshafima Rasit Ali[1,*], Nur Fathin Amirah Shafie[1,2], Mohd Yusof Hamzah[2], Zatil Izzah Tarmizi[1]

[1] Department of Chemical and Environmental Engineering, Malaysia-Japan International Institute of Technology, Universiti Teknologi Malaysia, Kuala Lumpur, Malaysia
[2] Radiation Processing Technology Division, Malaysian Nuclear Agency, Selangor, Malaysia

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ABSTRACT

PDA monomers typically self-assemble into vesicles in water. In this form, they acquire a novel property, where they can respond to various stimulants, including radiation exposure, that can be useful for colorimetric sensing applications. The quality of its response depends on its processing parameters. Therefore, optimising critical parameters such as monomer concentration, temperature and solvent ratio is essential. Herewith, the Box-Behnken Design (BBD) model was employed. Monomer concentration was set between 1 to 2mM; processing temperature was set between 25 to 65°C, and chloroform/THF ratio was set between 0 to 100. The responses obtained from the combinations were measured based on the PDA optical absorbance upon gamma radiation stimulation. It was found that PDA vesicles processed with 2.0 mM monomer concentration in a 50:50 solvent ratio at 65˚C yield the best vesicle formation for colorimetric sensor application.

1. Introduction

Polydiacetylene (PDA) is a versatile material that has been used in the fast and straightforward sensor application [1,2] field due to its unique optical properties [3,4] and exhibits an intense blue color due to the absorption of light by the ene-yne poly-conjugated chain in the visible spectrum [1,5-9]. PDA can be formed by a 1, 4-addition reaction of diacetylene (DA) induced by UV irradiation at 254 nm [6] or γ irradiation of self-assembled DA. When the aligned monomer's backbone of PDA is disturbed by external stimuli, the energy gap between the highest occupied and lowest unoccupied molecular orbitals of overlapped p-orbitals increases, resulting in the conjugated backbone's absorption pattern and a blue to red colorimetric change [1,6,10]. The distorted backbone of PDA exhibits fluorescence in addition to colour change, allowing the optical properties of PDA to be characterised by changes in the absorption spectrum and fluorescence intensity [1,2,11,12]. In this study, the polydiacetylenes vesicles produced can be formed in a variety of

* *Corresponding author.*
E-mail address: roshafima@utm.my

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conditions such as concentration, pH, temperature, solvent types, and so on, and several condition values must be determined to identify the optimal condition of prepared samples [6,7,13-16]. As a result, the authors of this study sought to investigate alternative methods for reducing the number of experiments required to prepare polydiacetylene vesicles.

In recent years, response surface methodology (RSM) has been one of the most widely used methodologies for statistically quantifying the effects of the relationship between parameters and responses in the analysed process, resulting in identifying the parameters and characteristics that allow the process to become optimal. To optimise the responses of polydiacetylene vesicles, designs such as Doehlert Design [17-18], Box-Behnken Design (BBD) [19-21], or Central-Composite Design [22-23] can be used. The need for a proper design saves a lot of time and considers the interactions between the factors [22]. It obtains satisfactory separation and values for the dependent variables. The full factorial design, on the other hand, included numerous experiments. The main benefit of this analysis was that it reduced the number of experiments. BBD does not include combinations where all variables are at their maximum or minimum values [21,24]. The PDA vesicles must be optimised because the responses of PDA vesicles produced under different conditions vary.

This study aims to find the optimal condition for preparing polydiacetylenes vesicles by controlling three parameters known as the concentration of the monomer, the temperature of the processing, and the solvent ratio used for the sample preparation. The synthesis experiment was carried out to confirm and determine the main factors affecting the optimal condition of producing polydiacetylenes vesicles. The Box-Behnken Design (BBD) method was employed in this work to optimise polydiacetylene vesicles using three parameters. The combinations of the three variables resulted in PDA vesicles of various conditions. The vesicles were then subjected to gamma radiation for stimulation. Responses obtained from the stimulation were analysed for its optical absorbance was measured.

2. Methodology

2.1 Materials

Commercially obtainable diacetylene monomer 10, 12-pentacosadiynoic acid (PCDA-Sigma Aldrich) was purchased and used without further purification. R & M Chemicals supplied chloroform (with 0.6-1.0% ethanol) with a molecular weight of 119.38 g/mol, was used as received. Tetrahydrofuran (THF) with a molecular weight of 72.11 g/mol was obtained from Sigma-Aldrich and used as received. Throughout the experiment, deionized water was used.

2.2 *Preparation of Polydiacetylenes Vesicles*

PCDA monomer was dissolved in a round-bottom reaction flask at different solvent mixture ratios. The solvents were removed after 5 hours of moderate heating in a vacuum oven at 50°C. The flasks containing the PCDA solution were occasionally turned on each side to ensure thin film formation on the glass surface. The flask was then, added with deionised water to reach a total lipid concentration of 1 to 2 mM. The mixtures were then heated from 45°C to 65°C and sonicated until a homogeneous turbid solution formed. The liposome dispersion was centrifuged (3000 rpm, 30 minutes) to separate aggregates. Large clumps and undissolved particles at the tube's bottom were discarded. The liposome dispersion produced by the process was irradiated with 3kGy of gamma-ray. Sample absorbances were measured using the Shimadzu UV-1700 UV-Vis spectrometer in the 200-700 nm wavelength range.

2.3 Box-Behnken Design (BBD) of Experiments

Experiment designs focused on the Box-Behnken principle can be used to model the response surface. These designs do not employ full or fractional factorial designs. The design points are located in the centre of the dimension k-1 subareas. In the case of three factors, for example, the points are located in the centre of the experimental domain's edges. These designs involve three levels for each factor. The three-factor BBD does not satisfy the iso-variance per rotation requirement. The BBD is a useful tool for optimising the UV-Vis Spectroscopy analysis. This study aimed to identify the most important factors that influenced the variables [22].

Three variables were studied using the BBD method: monomer concentration, processing temperature, and solvent ratio between chloroform and THF. The experimental ranges and levels of the independent variables of the BBD method for polydiacetylene vesicles are shown in Table 1. The minimum number is -1 for the lowest value of each factor and the maximum number is 1 for the highest value of each factor involved.

Table 1
Experimental ranges and levels of the independent variables

	-1	0	1
Concentration	1	1.5	2
Temperature	25	45	65
Solvent ratio used	0	50	100

3. Results and Discussion

3.1 Optimization of Parameters for Formation of Polydiacetylenes Vesicles Process

The interaction and relationships between independent and dependent variables were investigated using a scientific and systemic approach to experimental design. The Design Expert® software (Version 11.1.2.0, Stat-Ease Inc., Minneapolis, USA) was employed to optimise peak absorbance. Optimization studies were conducted with independent variables (concentration, temperature, and solvent ratio) as variable factors, which were chosen based on the results of developmental experiments.

The absorbance value was used as a response variable. In total 15 experiments with three main factors were performed. The complete experimental design matrix and the responses based on experiments proposed by BBD for polydiacetylene vesicles are given in Table 2. According to the table, run order 5 has the highest peak compared to the other run orders. The obtained results show that the monomer concentration is higher, at 2 mM, the processing temperature is also higher, at 65°C, and the volume of solvent ratio is 50:50 between chloroform and tetrahydrofuran.

Table 2
Optimization of run orders for polydiacetylene vesicles

Run Order	Concentration	Temperature	Solvent ratio used	Absorbance
1	1.5	65	0	1.757
2	1.5	25	0	0.877
3	2	25	50	0.315
4	2	45	0	2.177
5	2	65	50	2.523
6	1.5	25	100	0.304
7	1	45	100	-0.001
8	1.5	45	50	0.281
9	1.5	65	100	0.642
10	1.5	45	50	-0.013
11	2	45	100	0.039
12	1.5	45	50	-0.013
13	1	65	50	0.689
14	1	25	50	0.075
15	1	45	0	2.371

3.2 Effect of Variables (Monomer Concentration, Processing Temperature and Solvent Ratio Used)

According to the hypothesis, higher monomer concentrations and temperature processing will promote higher polymerisation during radiation [25]. Increased polymerisation of PDA vesicles directly results in increased absorbance [26]. Based on the volume of solvent ratio between chloroform and tetrahydrofuran, the 50:50 ratio results in higher absorbance than the other ratios.

The normality test generates a typical probability plot and conducts a hypothesis test to determine whether or not the observations follow a normal distribution [27,28]. As shown in Figure 1, the blue dot was a response that reflected a similar trend with normal distribution conditions (red line). The blue points on the standard probability plot that fall along the straight line indicate that the absorbance distribution would be a great option for this analysis [26]. Model performance figures can be applied to these records.

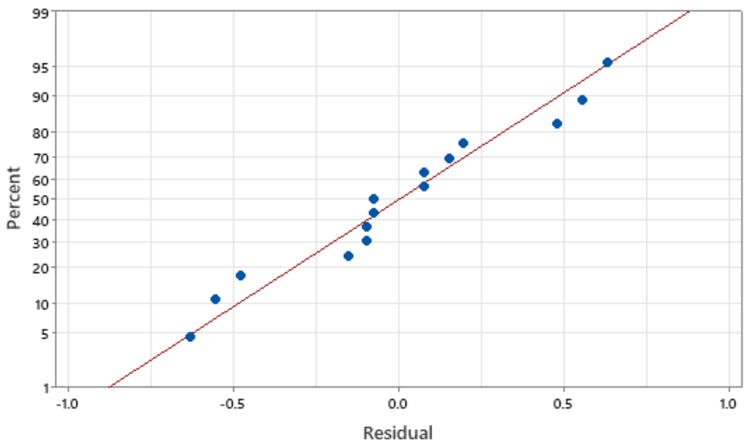


Fig. 1. Normal probability plot

Figure 2 illustrates the Pareto charts of the significant terms of factors and their interactions to explain the responses (concentration, temperature, and solvent ratio). The important terms were above the red line, while the non-significant terms were below it [29]. The primary goal of screening designs is to identify the most critical variables influencing response. Pareto charts can help to identify these influencing factors by comparing relative magnitude effects and determining their statistical significance. The Pareto chart displays the absolute values of the standardized impacts from largest to smallest. A reference line (red line at 2.571) indicates that factors and variables beyond it may be significant [30]. According to the Pareto chart results, the solvent ratio used (C) was the most important operational variable, indicating that the absorbance peak of the polydiacetylene vesicles increased.

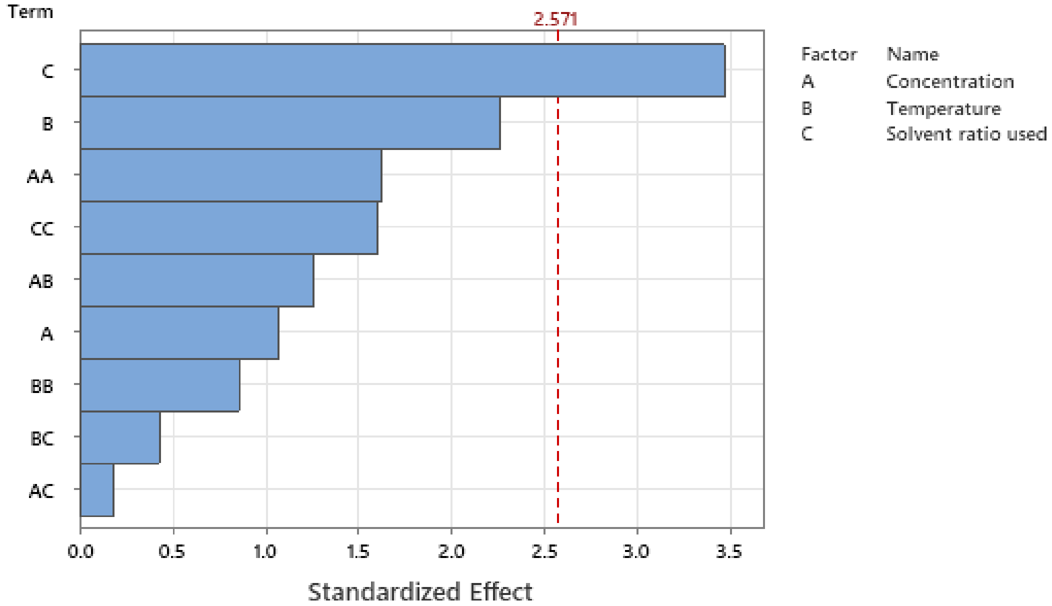
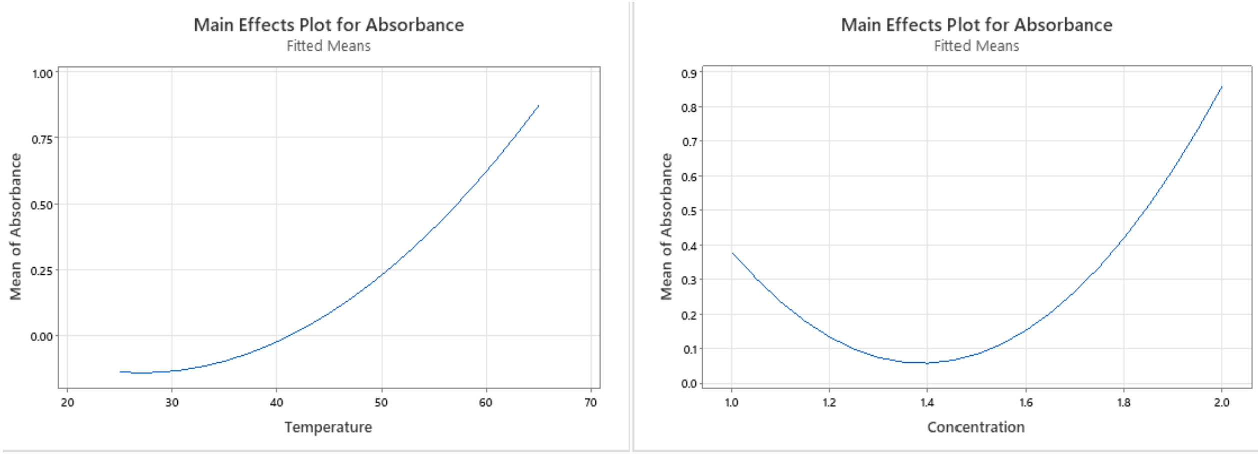


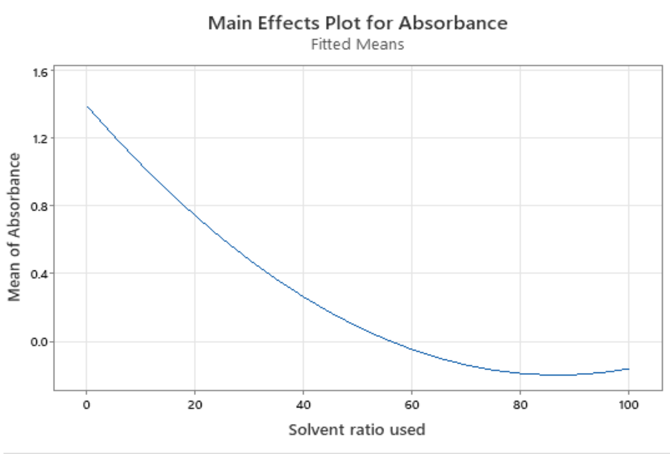
Fig. 2. Pareto chart of standardized effects of the factors and interactions for polydiacetylene vesicles

Interaction Analysis is one of the functions of Box-Behnken Design that can be used to find an optimal formation of polydiacetylenes vesicles by varying the concentration of the monomers, processing temperature and solvent ratio of the polydiacetylenes vesicles used. According to the interaction analysis (Figure 3), increasing the concentration and temperature produced good outcomes for the variables' relationships. The concentration, temperature and solvent ratio can be set to 2.0 mM, 65° C and 50:50 to achieve highest PDA absorbance peak.

A cube plot is used in the study to determine the best process factors for achieving optimal absorbances [31]. The resulting polydiacetylene vesicles in solution are proportional to the absorbance peak. A higher absorbance peak indicates the formation of more polydiacetylene vesicles. As a result, the condition that produces the higher absorbance peak value is advantageous. In this case, the absorbance peak with the highest absorbance was preferred. The absorbance peak appeared to be highest in the monomer solution irradiated with the highest polydiacetylene concentration (Figure 4). At this point, the highest variation of producing PDA vesicles, which was at 2.0 mM concentration, 65°C processing temperature and 50:50 volume solvent ratio (chloroform to tetrahydrofuran) was preferred because it had a significant influence on the quality of the PDA vesicles produced.



(a) (b)



(c)

Fig. 3. Interaction Analysis: (a) Absorbance *vs* temperature (b) Absorbance *vs* concentration and (c) Absorbance *vs* solvent ratio used

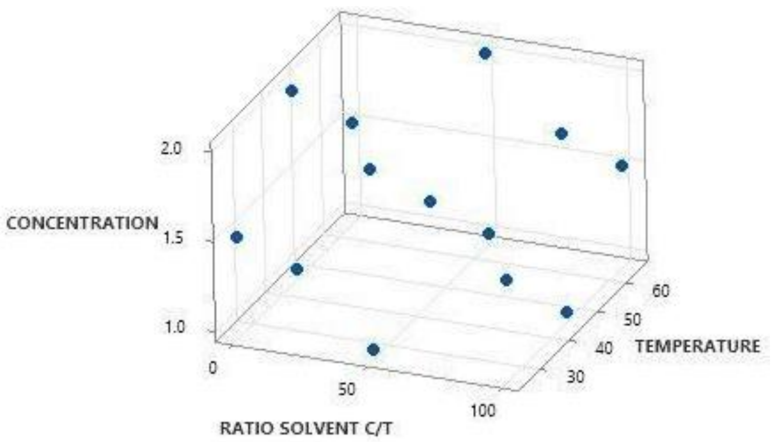


Fig. 4. Cube plot; 3D scatterplot of concentration *vs* temperature *vs* ratio solvent C/T

Contour plots were also used to visualize the effects of the parameters on the chosen absorbance response. The contour plot analysis showed that the maximum absorbance peak demonstrated these factors' non-linear effects on the selected response [32]. Based on the contour plots in Figure 5, the area of colour with the highest absorbance value, 2.523, is the optimum condition obtained depending on hypothesis. The higher the concentration and temperature, the higher the absorbance peak produced by polydiacetylene vesicles.

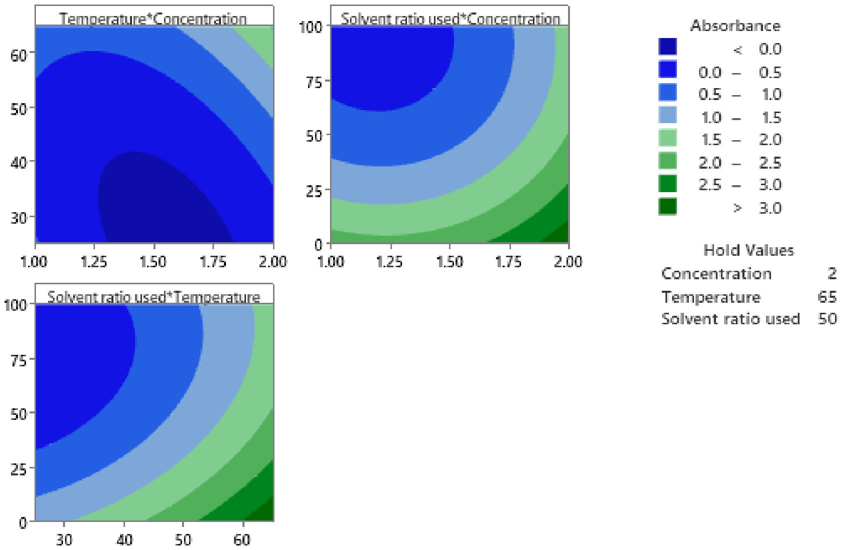


Fig. 5. Contour plot for each variable

3.3 Optimum Parameter

The best reaction conditions for polydiacetylene cysts were found and validated. The results showed that polydiacetylene vesicles produced (using 15 different combinations of reaction conditions) had the highest absorbance peak. Peak absorbance is a response to the BBD method variables used in this study. The following criteria were fixed for the reactions: monomer concentration, processing temperature and solvent ratio used to produce the optimal condition of the polydiacetylene vesicles. The optimum conditions proposed were reaction concentration at 2 mM, reaction temperature of processing at 65°C and a volume of solvent ratio of 50:50. As a result, it is determined that the sample with the highest concentration of monomer and processing temperature is the optimal condition selected in this study.

4. Conclusions

The PDA optimization *via* BBD method has successfully presented a set of optimum parameters consisting of monomer concentration, processing temperature, and the solvent ratio chloroform to the THF; possible for the maximum colorimetric effect. The optimization study concluded that the highest amount of monomer resulted in high monomer polymerisation. The condition was also influenced by the temperature of the process, where more activation energy was available at higher temperatures to promote the polymerisation process. However, there is no clear winner on the type of solvent, as an equal mixture of THF and chloroform shows the highest optical result. Overall, the optimum condition reported here can be the basis for preparing an excellent colorimetric sensor.

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