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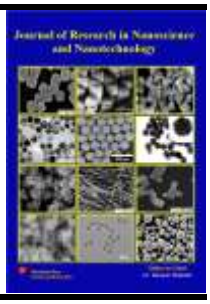

# Full Factorial Design: Optimization for Nanogel Formation

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**ABSTRACT**

The Design of Experiments, DoE, is a set of applied statistics tools for systematically classifying and quantifying cause and effect relationships between variables and outputs in the studied process, which may lead to the discovery of the settings and conditions under which the process becomes optimized. By investigating multiple combinations of factor levels simultaneously, Full Factorial Design can reduce the number of experiments required. The concentration of nanogels in a solution is proportional to the intensity of photon scattering rates. As a result, the condition that produces the higher count rate value is preferable. This study employs a Full Factorial Design to determine the optimal irradiation dosage and DMAEMA concentration for P(NIPAAM-PVP-PEGDA-DMAEMA) nanogels.

*Keywords:*
Full Factorial Design, Optimization, Nanogel, DMAEMA

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## 1. Introduction

The need for DoE in pharmaceutical process development has grown dramatically over the last decade [1] as DoE reduces the number of experiments and provides precise output information compared to the conventional single-factor, OFAT (one-factor-at-a-time) experiment [2,3]. The most significant benefit of using DoE is quickly detecting how interactions between factors affect product yield and quality. This method aids in quantifying the effects of each factor on the potential outcome [4,5]. However, the more runs performed in the DoE, the greater the budget and time required. Full Factorial Designs are the most used method [6] as the number of experiments can be reduced compared to other DoE experiments. In each complete trial or replication of the experiments, Full

Factorial Designs generate experimental points by combining all possible combinations of the levels of the factors [7].

A thorough understanding of the relationships between input factors and product quality is the key to improving the performance of nanogels and generating desirable drug delivery products. The application of Dynamic Light Scattering, DLS, is well-established for evaluating the diffusion coefficient of dispersed particles in a liquid by measuring fluctuations in the intensity of scattered light using the correlation function provoked by particles' random, disordered motion caused by random collisions with solvent or gas molecules, [8-10] known as Brownian motion. As a result, information about the size distribution of particles could be acquired by processing the fluctuations of the intensity of scattered light. Furthermore, the concentration of nanogels in the solution might influence the intensity of photon scattering or countrates [11].

DMAEMA or 2-(Dimethylamino)Ethyl Methacrylate is one of the most studied temperatures and pH-responsive polymers, as its LCST value is adjacent to the body temperature [12]. Thus, DMAEMA is a rigid substrate for various applications, including drug delivery systems. Several studies have been performed to fortify the thermo-sensitivity of copolymerized DMAEMA nanogel. Wang and colleagues discovered that their P(NIPAAm-co-DMAEMA) copolymerized hydrogels had a high thermo-sensitivity, as evidenced by their fast deswelling rate and visible LCSTs with remarkable pH and temperature-sensitive features [13]. Motaali *et al.*, [14] also discovered that their (NIPAAM–DMAEMA)–$Fe_3O_4$ polymer created via free-radical emulsion polymerization could be employed for regulated drug delivery due to its thermal/pH sensitivity. In aqueous media, the poly(ethylene oxide)-b-PDMAEMA-b-PNIPAAm) copolymer polymerized via surface-initiated reversible addition-fragmentation chain transfer (RAFT) demonstrated dual temperature and pH sensitivity [15].

According to the literature [16-20], adding amide and carbonyl groups to the main chain of thermo-responsive nanogels will increase hydrogen bonding and LCST. Thus, the influence of DMAEMA concentration on the nanogels based on N-isopropyl Acrylamide (NIPAAM), Vinylpyrrolidone (VP) and Poly (Ethylene Glycol) Diacrylate (PEGDA) by gamma ($\gamma$) radiation-induced polymerization was investigated in the study. Herein, we present the synthesized experiment to validate and identify the main effects influencing the optimum P(NIPAAM-VP-PEGDA-DMAEMA) nanogels condition via full factorial design as an alternative to the conventional OFAT methods. Two (2) parameters were studied at 2-levels full factorial design. The response of interest is count rates, which are determined by DLS.

## 2. Methodology

### *2.1. Materials*

NIPAAM, 99%, PVP, 99%, PEGDA, and 98% DMAEMA were purchased from Sigma-Aldrich and used without prior purification. Ultrapure water was used throughout this work for all solution preparations.

### *2.2. Synthesis of Thermosensitive Nanogel*

NIPAAM, PVP, PEGDA and DMAEMA were dissolved in water at specific molar ratios as previous study [21]. The mixture was aliquoted into several vessels and had its oxygen content purged with nitrogen gas 30 min prior to $\gamma$-irradiation. Each vessel was irradiated at 5, 10, 15 and 20 kGy. After irradiation, the P(NIPAAM-PVP-PEGDA-DMAEMA) nanogels were purged with nitrogen gas for 30 min. Then, the P(NIPAAM-PVP-PEGDA-DMAEMA) nanogels were dialyzed

against water using a 12,000 Da molecular cutoff membrane for 48 h. The dialysis procedure was monitored using Shimadzu UV-1700 at 280 nm wavelength. It was then lyophilized and resuspended in ultrapure water for subsequent characterization and testing. The samples were diluted into different concentrations.

### *2.3. Full Factorial Design*

A two-level full factorial design was used to run 12 simulation cases. In this 2-factor, 2-level randomized full factorial design, two factors were evaluated at two levels each, and experimental trials were conducted at all four possible combinations with three replications. In the current study, the results of Full Factorial Designs, namely the Normal Probability Plot, Pareto Chart, Interaction Analysis and Cube Plot, were used to determine the optimum level and significant operational variables.

### *2.4. Dynamic Light Scattering Study*

Dynamic light scattering measurement was performed to obtain the size (hydrodynamic diameter) and photon scattering intensity of the resulting nanogel. The equipment used was Nanophox from Sympatec GmbH, a 10 mW HeNe laser beam at a wavelength of 632.8 nm and a 90° scattering angle at 25°C. The measurement condition was set according to previous reports. The lyophilized nanogel and the loaded nanogel were redispersed in ultrapure water and filtered with a 0.22 μM pore size filter. Measurement was done using the 3D cross-correlation function on the scattering intensity and analyzed using cumulant analysis to obtain the particles' hydrodynamic diameter and dispersity information.

## 3. Results and Discussion

### *3.1. Synthesis and Characterization of Thermosensitive Nanogel*

The irradiated polymeric mixture of P(NIPAAM-PVP-PEGDA-DMAEMA) nanogel was expected to produce random copolymers as the thru effect on the polymers in the solution was negligible upon irradiation (Figure 1). The grafted polymeric structures were estimated to be random with an amphiphilic characteristic of the hydrophobic core and hydrophilic shell. The proposed copolymer structure is shown in Figure 2.

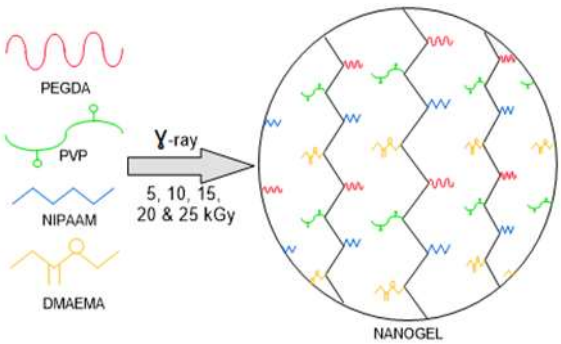


**Fig. 1.** Synthesis of P(NIPAAM-PVP-PEGDA-DMAEMA) Nanogel

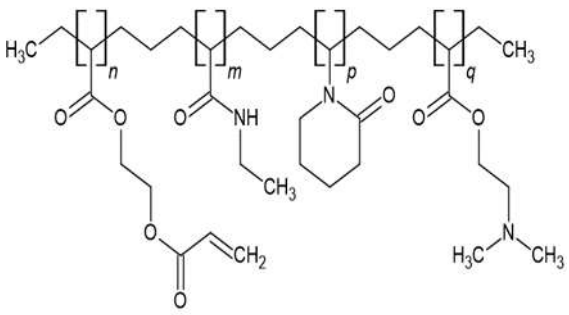


**Fig. 2.** Suggested copolymer structure of P(NIPAAM-PVP-PEGDA-DMAEMA) Nanogel from the Gamma-Induced Copolymerisation Reaction

### 3.2. Optimization of Nanogels Production Process

The interaction and relationships between independent and dependent variables were investigated using a scientific and systemic approach to experimental design [22,23]. The software tool Design Expert® (Version 11.1.2.0, Stat-Ease Inc., Minneapolis, USA) was used to optimize count rates based on nanogels. Optimization studies with $2^2$ full factorial designs (2-factor, 2-level) were carried out using independent variables ($\gamma$-irradiation doses and DMAEMA concentration ratio) as variable factors and keeping the concentration of other raw materials constant, which were selected based on the results of developmental trials. Count rates were taken as response variables to investigate the effect of independent variables.

#### 3.2.1 Normal probability plot

To determine whether or not the observations follow a normal distribution, the normality test generates a normal probability plot and conducts a hypothesis test [24]. The blue dot was a response that reflected a similar trend with normal distribution conditions (red line), as illustrated in Figure 3. The blue points falling along the straight line on the normal probability plot indicate that the count rates distribution would be a good choice when running this analysis [4,25]. The process capability statistics are now applicable to this data.

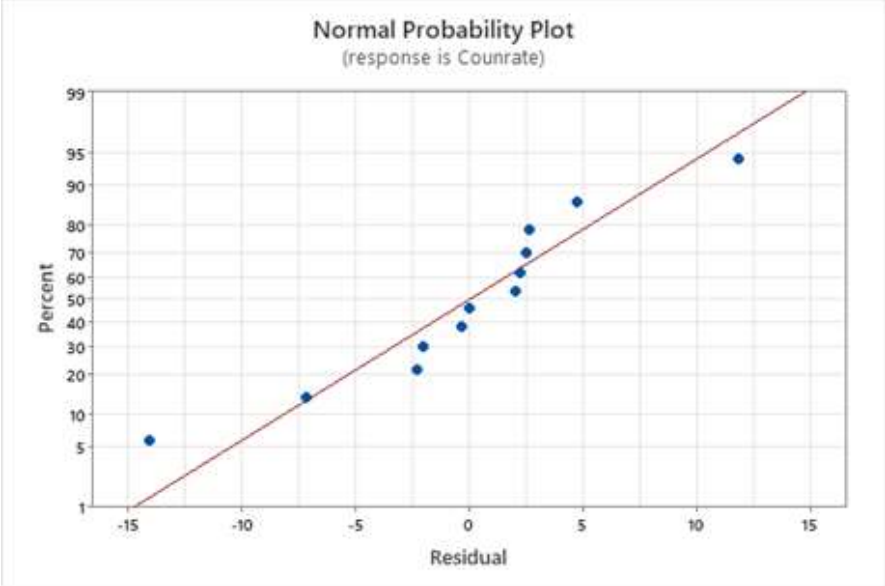


**Fig. 3.** Normal probability plot

#### 3.2.2 Pareto chart plot

The primary goal of screening designs is to identify the key variables influencing response. Pareto charts aid in identifying these influential factors by comparing the effects of relative magnitude and evaluating their statistical significance [26]. The Pareto chart displays the absolute values of the standardized effects from largest to smallest. A reference line indicates that the factors and variables that extend beyond this line may be significant (Figure 4). The significant operational variables for achieving a high response of the count rates obtained from the Pareto chart (Figure 4) were the DMAEMA ratio concentration and $\gamma$-irradiation dosage. The results revealed that the DMAEMA concentration was the most significant operational variable compared to the $\gamma$-irradiation dose factor,

indicating that the hydrophilic DMAEMA contributes to enhancing hydrogen bonding and raising the LCST.

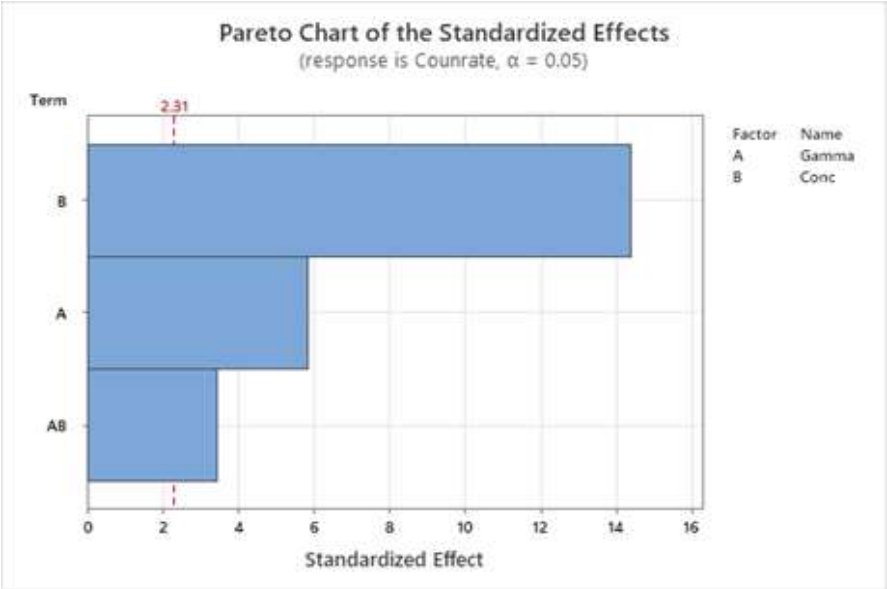


**Fig. 4.** Pareto chart plot

*3.2.3 Interaction analysis*

Interaction Analysis is one of the functions of Full Factorial Design that can be used to find the optimum formation of P(NIPAAM-PVP-PEGDA-DMAEMA) nanogels by varying the concentration of mixtures and γ-irradiation doses. According to the interaction analysis (Figure 5), the γ-doses and DMAEMA concentration ratio should be set at 20 kGy and the highest DMAEMA concentration ratio to achieve the maximum scattering intensity of 104.69 kcps. It is consistent with the hypothesis that adding DMAEMA, or the amide and carbonyl groups, to the main chain of thermo-responsive nanogels increase hydrogen bonding [17]. As a result, the thermal breakage of the hydrogen bond between NIPAAM amide groups inside polymer chains and water molecules increases, leading to an increase in LCST. As the temperature rises over the LCST, the hydrophobic hydrogen bonds in the polymer backbone weaken, become partially dehydrated, and can no longer be solubilized, causing the polymer to collapse [27,28].

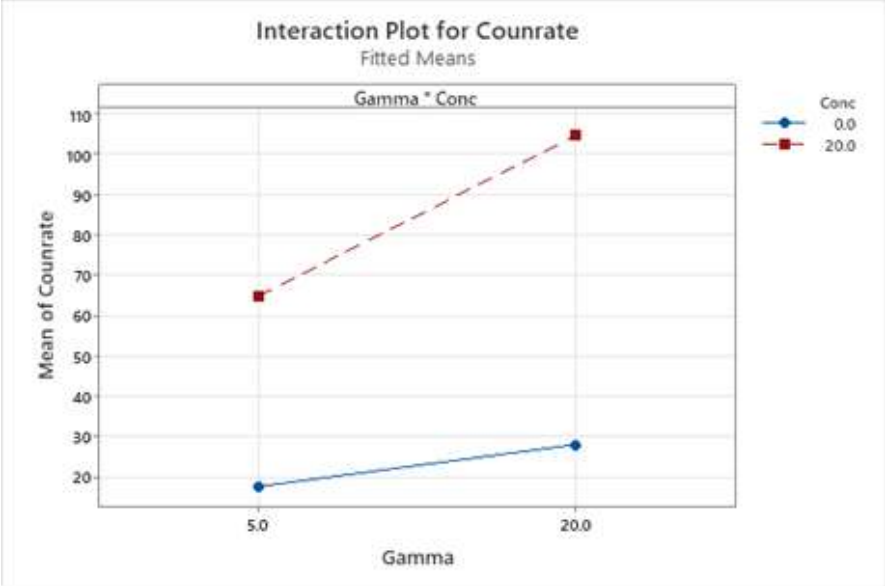


**Fig. 5.** Interaction analysis

*3.2.4 Cube Plot*

A cube plot determines the best process factors to achieve optimal count rates in the study. The resulting nanogels in the solution are directly related to the intensity of photon scattering or count rates [11,29]. A higher scattering rate (kcps) or count rates indicates more nanogels produced. Therefore, the condition that yields the higher scattering rate value is favourable. In this scenario, the highest count rate was preferred. The monomer solution irradiated at 20 kGy with the highest DMAEMA concentration ratio seemed to have the highest photon scattering rate of 104.69 kcps (Figure 6). The result is consistent with the findings of Shakoori *et al.*, [17], who claimed that increasing the DMAEMA moiety in the reaction made the copolymer more hydrophilic by forming more hydrogen bonds between the polymer chains and water molecules [30], resulting in a higher LCST.

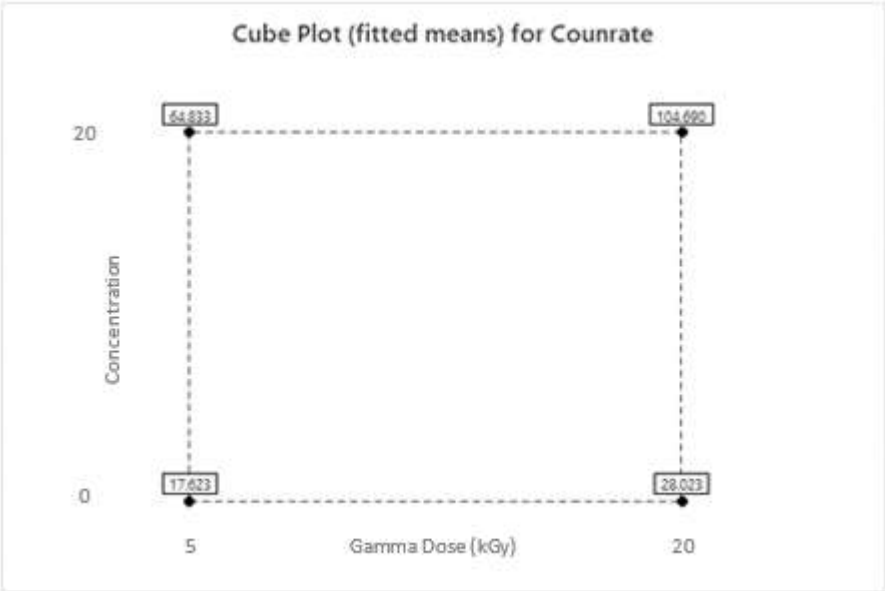


**Fig. 6.** Cube plot

### 3.3. Dynamic Light Scattering Study

The size of the P(NIPAAM-PVP-PEGDA-DMAEMA) nanogels increased at higher irradiation doses (Figure 7a), which is consistent with nanogel aggregation [31]. The increase is due to the polymerization of the P(NIPAAM-PVP-PEGDA-DMAEMA) nanogels. The surface energy of the P(NIPAAM-PVP-PEGDA-DMAEMA) nanogels plays a key role in situating the atoms and the chosen polymer once they interrelate with the high energy of γ-rays [32,33]. Similarly, Kozlovskiy and associates [34] determined that an escalation in the γ-irradiation dose influences polymer size enlargement.

Furthermore, DLS results show that as the concentration of DMAEMA increased, the size of the P(NIPAAM-PVP-PEGDA-DMAEMA) nanogels decreased (Figure 7b). The sample with the highest concentration of DMAEMA had the smallest nanogels, measuring 134 nm to 223 nm. These were in the ideal size range for nanogel in drug delivery applications, 70-200 nm [35]. The hydrophilicity of DMAEMA in the DMAEMA-NIPAAM copolymer composition increased as the temperature rose, resulting in a higher LCST and swelling ratio [13,36]. As a result, it is determined that the sample with the highest concentration of DMAEMA and highest γ-irradiation dose is the optimal concentration chosen in this study.

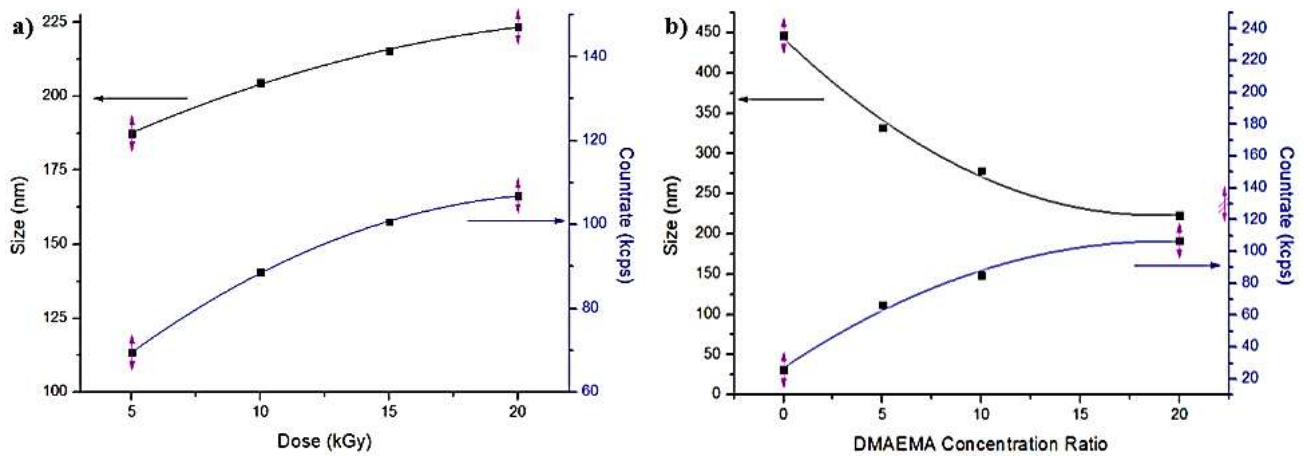


**Fig. 7.** Dynamic light scattering intensities and size of P(NIPAAM-PVP-PEGDA-DMAEMA) Nanogels as Functions of a) Irradiation Dose and b) DMAEMA Concentration Ratio.

## 4. Conclusions

In this study, an increasing DMAEMA concentration ratio of P(NIPAAM-PVP-PEGDA-DMAEMA) nanogels was synthesized and prepared in a single step using a carcinogenic-free and ecologically friendly γ-radiation-induced copolymerization technique. This study avoided the OFAT method because it is time-consuming and does not guarantee the optimal set of parameters. Instead, the full factorial design method was chosen. After all, it is much more reliable as it is based on a mathematical model of the combined effect of the processing factors. P(NIPAAM-PVP-PEGDA-DMAEMA) nanogel shows a promising material system and potential in the drug delivery system. The optimum irradiation dosage of P(NIPAAM-PVP-PEGDA-DMAEMA) nanogels for further investigation is 20 kGy, and the highest DMAEMA concentration appears to promote nanogel formation and shrinkage in the same formulation. Consequently, the nanogels derived under this condition will be used for further characterization and testing.

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