

## Research Article

# Optimization of Synthesis Parameters of Mesoporous Silica Nanoparticles Based on Ionic Liquid by Experimental Design and Its Application as a Drug Delivery Agent

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Optimization is a process utilized to discover the best condition to generate the best possible outcome. One of the common optimization method used in the field of chemistry is response surface methodology (RSM). This method consists of mathematical and statistical techniques which relate the responses with the variables of interest. There are many experimental designs in RSM, and one of the most common one is the Box-Behnken design (BBD). In this work, BBD was employed to analyze the main effects and interactions of the reaction temperature, amount of template, and amount of triethanolamine (TEA) on the two responses which are the surface area (SA) and particle size (PS) of ionic liquid templated mesoporous silica nanoparticles (MSNs). It was found that the SA and PS were fitted with linear and quadratic models, respectively. MSNs with the highest surface area ( $999.051 \text{ m}^2 \text{ g}^{-1}$ ) was chosen for the application of drug delivery; thus, drug loading and drug release experiments were conducted. From these studies, it was found that 37% of drug (quercetin) was successfully encapsulated in MSN and, in 48 hours, 32% of the drug was released.

## 1. Introduction

Mesoporous silica nanoparticles (MSNs) can be defined as silica materials within the size of nanometers that contain porosity. The term porosity was given according to the IUPAC classification when the pores with a diameter less than 2 nm, between 2 and 50 nm, and more than 50 nm are defined as micropores, mesoporous, and macroporous, respectively [1]. They garnered a lot of attention in various fields due to their properties such as easy manipulation of physical characteristic, inert, great biocompatibility, and easy functionalization. In general, the syntheses of MSNs involve two reactions which are hydrolysis and condensation processes under basic condition. The two most well-established

methods are modified Stöber and cocondensation methods. In Stöber and co-condensation methods, ammonia and sodium hydroxide (NaOH) solutions were utilized, respectively, as the bases and catalysts [2, 3]. Besides the base, the template and silica source are the two other main components in the synthesis process. The most commonly used silica source and template are tetraalkyl orthosilicate (TAOS) and surfactant or polymer, respectively.

Ionic liquids (ILs) can be defined as salts with a melting point below the boiling point of water [4]. ILs that are molten at room temperature are defined as room temperature ionic liquids (RTILs) [5]. They received a lot of attention in the field of green chemistry due to their properties such as essentially zero vapour pressure, high thermal stability, and

inflammability which minimize air pollution compared to organic solvents [1, 6, 7]. ILs consist of two core components, large organic cations and inorganic or organic anions [8]. Since the core components of ILs are similar to an anionic surfactant used in MSN synthesis, there is potential of utilizing ILs as templates in MSN synthesis.

MSN properties are susceptible to many factors, and these factors can be manipulated to obtain a product with targeted characteristics. Therefore, it is important to identify the synthesis parameters that influence the MSN properties. Some of the most commonly manipulated synthesis parameters are the amount of template, amount of base, and reaction temperature. Yamada et al. (2014) studied the effect of concentration of template in preparation of colloidal MSNs, and they found colloidal MSNs were generated at higher template concentration. This was due to dual function of the template which serves as a porosity agent and dispersant [9]. Chen and coworkers discover that in cases where the concentration of surfactant is too low, the formation of a nonporous wall layer occurred due to excess silica source [10]. Therefore, it is important to control the ratio between the template and silica source in order to overcome the problems which occurred at a certain condition. Lv and coworkers use triethanolamine (TEA) as the catalyst, and they studied the effect of TEA amount on the morphology of MSNs. It was observed that as the amount of TEA increased, the particle size (PS) decreases [11]. Besides that, temperature is another parameter that is frequently being studied in the MSN synthesis and this is due to the thermodynamics and kinetics of the reaction dependent on reaction temperature [10]. It was found from many researches that MSNs' PS increased with increasing reaction temperature.

In the field of chemistry, an optimization process is normally used to discover the best condition to generate the best possible outcome. The traditional method of optimization is known as one variable at a time where one parameter was varied while the other parameters were kept constant. There are two major disadvantages with this method. First, it does not include the effect of variable interaction and the second is the large number of experiment which leads to the increase of time and cost [12]. In order to overcome this problem, multivariate optimization systems were developed and the most commonly used is Response Surface Methodology (RSM). This method consists of mathematical and statistical techniques which relate the response with the variables of interest [13].

Application of MSNs varied across fields, but in these recent decades, its application focuses towards biomedical field. In contrast to its micrometer or larger dimensions, MSNs exhibit unique properties which are favorable for various functions. For biomedical purposes, some of the attractive properties of MSNs are high loading capacity, easy size, shape and pore tailoring, low toxicity, chemical inertness, and easy functionalization [14]. Furthermore, this material is easy to synthesize and scalable for large productions [15]. One of the greatest breakthroughs of using MSNs as a drug delivery agent was creating a stimuli-responsive controlled release system based on this material. The basis of the controlled release system is to create a material that can be activated to release the drug at a

TABLE 1: Uncoded and coded levels of the independent variables of MSN synthesis.

Independent variables	Symbol	Levels		
		-1	0	+1
Amount of template (g)	$X_1$	0.50	0.75	1.00
Amount of TEA (g)	$X_2$	0.06	0.13	0.20
Temperature ( $^{\circ}\text{C}$ )	$X_3$	40	65	90

targeted area using certain stimuli. Lin and coworkers were the first to develop this system in the year 2003, and the system was based on MCM-41-type MSNs. The guest molecules were loaded into the pores of MCM-41, and the open ends of the pores were closed using cadmium sulphur (CdS) nanoparticles via breakable disulphide linkage [16].

In this study, a Box-Behnken Design (BBD) was used to analyze the influence of the amount of template, amount of base, and reaction temperature on the surface area (SA) and PS of ionic liquid templated MSNs. From the result obtained, the MSN with the highest surface area was chosen to undergo drug loading and drug release process. This is to study its capability as a drug delivery agent.

## 2. Materials and Method

*2.1. Materials.* All chemicals used in the experiments were of analytical grade and used without further purification.

*2.2. Synthesis of MSNs.* This method was adapted and modified from Lv and coworkers and Mohamed Isa and associates [11, 17]. In a 100 mL round bottom flask, 1-hexadecylpyridinium bromide ( $\text{C}_{16}\text{PyBr}$ ) (0.5-1.0 g), deionized water (20 mL), and triethanolamine (TEA) (0.06-0.20 g) were added and the mixture was stirred for 1 hour (40-90 $^{\circ}\text{C}$ ). Tetraethyl orthosilicate (TEOS) (1.5 mL) was added dropwise to the mixture, and it was stirred for another hour (40-90 $^{\circ}\text{C}$ ). After cooling to room temperature, the product was collected via centrifugation at 12 000 RPM for 30 minutes. The product was washed once with water followed by ethanol. To remove the template, the solid was dispersed in ethanol (60 mL) via sonication followed by the addition of concentrated hydrochloric acid (HCl) (3 mL). The mixture was then refluxed overnight. The template-removed product was collected via centrifugation, and the solid obtained was rinsed with ethanol twice. The solid was dried in an oven at 50 $^{\circ}\text{C}$  for at least 12 hours.

*2.3. Experimental Design.* A BBD was employed to analyze the main effects and interactions of the reaction temperature, amount of template, and amount of TEA on the responses SA and PS. The independent variables and their levels are shown in Table 1. A total of 13 experimental runs were carried out. The data obtained were analyzed using Design Expert 7.1.6 software by Stat-Ease Inc.

*2.4. Drug Loading.* Evaporation technique was chosen to load a drug, quercetin (Q), to the MSNs [18]. In an evaporation flask, MSN (100 mg) and Q (50 mg) were placed into it.

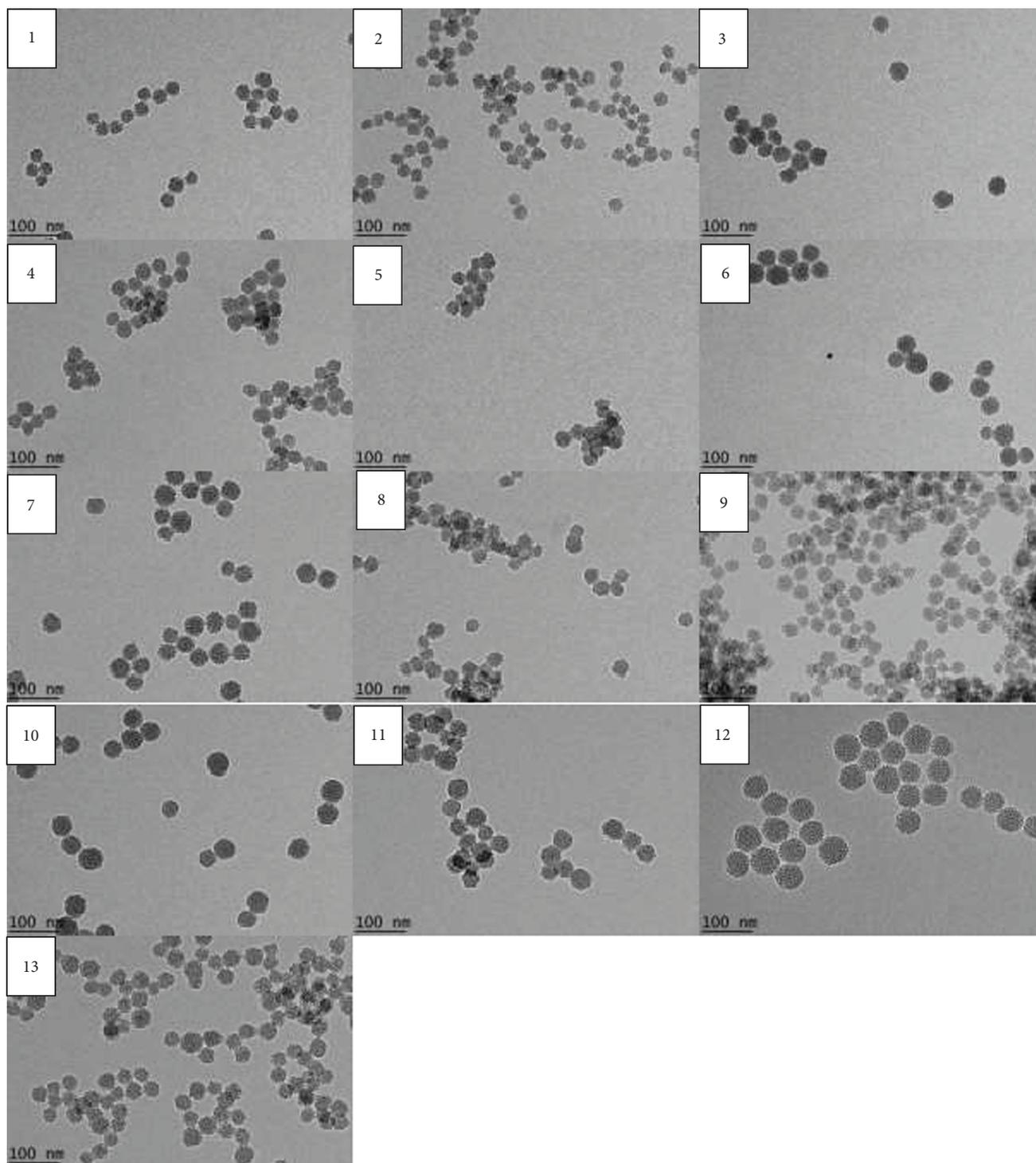


FIGURE 1: TEM images of MSNs synthesized corresponding to the runs (Table 1).

Ethanol (15 mL) was added into the flask, and the mixture was sonicated for 10 minutes using a bath sonicator. The solvent was then removed via rotary evaporation to obtain a Q-loaded sample which was designated as MSN-Q.

**2.5. Drug Release.** The drug release was evaluated using a dialysis bag technique [18]. The media used for this study is a mixture of PBS and ethanol with a ratio of 7:3. MSN-Q

equivalent to 1 mg of Q was weighed and dispersed in media. The dispersed sample was placed in a dialysis bag and was immersed into 9 mL of media with continuous stirring. At predetermined time intervals, 1 mL of samples was withdrawn and immediately replaced with an equal volume of fresh media to keep the volume constant. The samples were then properly diluted and analyzed at 380 nm using a UV-Vis spectrophotometer.

**2.6. Calibration Curve.** Stock solution with a Q concentration of 2 mg/mL was prepared using PBS and ethanol solution with a ratio of 7 : 3. A series of solutions with different Q concentrations was prepared by diluting the appropriate volume of stock solution. The solutions were then analyzed using a UV-Vis spectrophotometer at 380 nm, and the calibration curve was plotted.

**2.7. Characterization.** Transmission electron micrographs (TEM) were recorded on Tecnai G2 F20 operating at 200 kV. Samples were dispersed in ethanol under ultrasonication for 20 minutes. One droplet of suspension was applied to a 400-mesh carbon-coated copper grid and dried in air. The Brunauer-Emmett-Teller (BET) SA of the MSNs was measured by physisorption of N<sub>2</sub> at 77 K over a Micromeritics TriStar II 3020. TGA was conducted on TGA/SDTA 851 Mettler Toledo. The analyses were carried out at a heating rate of 10°C/min from the temperature range of 50-800°C with a nitrogen flow rate of 50 mL/min. UV-Vis spectra were recorded on a Shimadzu H.U.V.1650 PC UV-Visible spectrophotometer along the wavelength range of 200-600 nm.

### 3. Results and Discussion

**3.1. Optimization of MSN Synthesis.** In this research, the MSNs were prepared using a pyridinium IL under basic condition. The base used was TEA, and it was able to produce well-dispersed particles. The MSN formation mechanism is similar to the classical nucleation theory. However, in MSN formation, the nucleations begin with the micelle of the template which means that it begins above critical micelle concentration. It is proposed that MSNs are formed via charged mechanism and this occurs between the cationic template's micelle (S<sup>+</sup>) and silicate oligomers (Γ) [11, 19]. Silicate oligomers formed through hydrolysis of TEOS and electrostatic interaction of it with cationic template's micelle serve as a building unit. Condensation of this building block leads to the formation of MSNs [11]. The TEM images (Figure 1) indicate that all the synthesized MSNs exhibited spherical morphology with worm-like pores.

The experimental parameters generated by BBD and the experimental response values obtained are tabulated in Table 2. The Design Expert 7.1.6 software was used to find the best fitted models for the experimental design. The three main factors being investigated were reaction temperature, amount of template, and amount of TEA. In order to determine the best fitted models, several factors in the analysis of variance (ANOVA) such as coefficient correlations ( $R^2$ ), adjusted coefficient correlations (adjusted  $R^2$ ),  $P$  value, and  $F$  value play important roles. It was found that the linear model and quadratic model show the best fit for the SA and PS, respectively. The equations are shown in

$$\begin{aligned} \text{SA} &= 1469.02 - 316.05X_1 - 6.51X_3, \\ \text{PS} &= 27.723 - 116.572X_2 + 0.075X_3 - 1.754X_2X_3 \\ &\quad + 623.776X_2^2 + 3.759 \times 10^{-3}X_3^2. \end{aligned} \quad (1)$$

From the analysis of variance (ANOVA) of the SA (Table 3), it was found that the parameter with the

TABLE 2: Independent variable of BBD with experimental and predicted results.

Run	Factor, X			Response, Y	
	$X_1$ (g)	$X_2$ (g)	$X_3$ (°C)	$Y_1$ (m <sup>2</sup> g <sup>-1</sup> )	$Y_2$ (nm)
1	0.50	0.13	40	999.051	28.509
2	1.00	0.13	40	900.743	28.561
3	0.75	0.06	40	963.307	35.769
4	0.75	0.20	40	900.979	29.126
5	0.50	0.06	65	851.025	39.189
6	1.00	0.06	65	790.197	38.563
7	0.50	0.20	65	879.385	31.153
8	1.00	0.20	65	572.769	29.859
9	0.75	0.13	65	842.823	32.234
10	0.50	0.13	90	707.369	41.457
11	1.00	0.13	90	541.023	37.409
12	0.75	0.06	90	509.548	52.292
13	0.75	0.20	90	705.054	33.373

$X_1$ : mass of IL;  $X_2$ : mass of TEA;  $X_3$ : temperature;  $Y_1$ : SA;  $Y_2$ : PS.

TABLE 3: ANOVA of the fitted linear equation for the SA of MSNs.

Source	Mean square	$F$ value	$P$ value
Model	8.731E <sup>4</sup>	17.94	<0.0001
$X_1$	4.994E <sup>4</sup>	10.26	0.0069
$X_3$	2.116E <sup>5</sup>	43.47	<0.0001
$R^2$	0.8054		
Adjusted $R^2$	0.7605		

strongest effect (highest  $F$  value) is the reaction temperature ( $P < 0.0001$ ) followed by the template amount ( $P = 0.0069$ ). However, the amount of TEA does not affect the SA as the  $P$  value is more than 0.05. The coefficient correlation ( $R^2$ ) is a measurement of the degree of fit, and the model that shows the closest value to 1 of  $R^2$  indicates a great fit [20]. The response SA exhibited an  $R^2$  value of 0.8054 and an adjusted  $R^2$  value of 0.7605 at 95% confidence level. Besides that, this linear model is significant as proven by a high  $F$  value (17.94) and low  $P$  value (<0.0001).

Figure 2 shows the one factor plot of factor on the SA response. SA response is affected by the mass of IL and temperature of the reaction. A larger amount of IL leads to lower SA values. This might be due to the lack of silicate oligomers to accommodate the increase of micelle cation thus leading to the formation of joint MSNs which produced a lower SA value. At lower temperature, a higher SA value was obtained and this was due to the domination of a particle nucleation process. More nuclei will lead to more particles; thus, smaller particles were generated. Small particles have higher SA values [21, 22]. However, between these two parameters, temperature has the biggest impact on the SA based on the  $F$  value obtained from ANOVA.

From the analysis of variance (ANOVA) of the PS (Table 4), it was found that the parameter with the

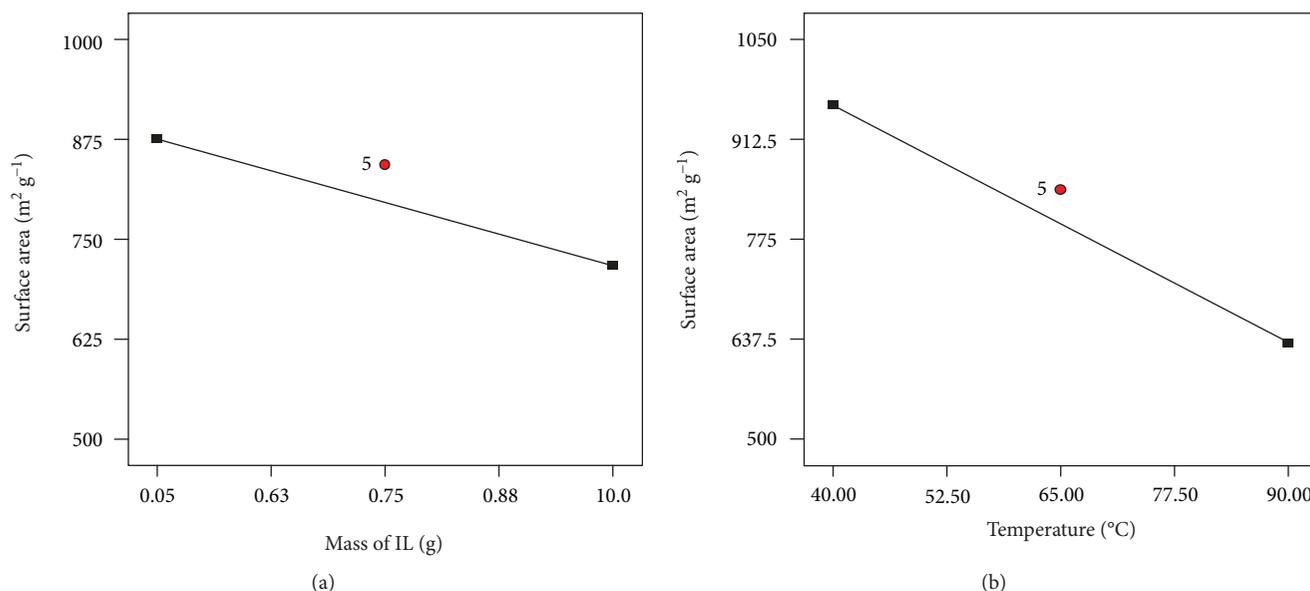


FIGURE 2: One factor plot for the (a) mass of IL and (b) temperature on the SA.

TABLE 4: ANOVA of the fitted linear equation for the SA of MSNs.

Source	Mean square	F value	P value
Model	$6.254E^1$	42.10	<0.0001
$X_2$	$2.237E^2$	150.57	<0.0001
$X_3$	$2.265E^2$	152.46	<0.0001
$X_2^2$	$3.934E^1$	26.48	0.0013
$X_3^2$	$2.324E^1$	15.65	0.0055
$X_2X_3$	$3.768E^1$	25.36	0.0015
$R^2$	0.9819		
Adjusted $R^2$	0.9585		

strongest effect (highest  $F$  value) is the reaction temperature ( $P < 0.0001$ ) followed by the TEA amount ( $P < 0.0001$ ). However, the amount of template does not affect the PS as the  $P$  value is more than 0.05. The response PS exhibited an  $R^2$  value of 0.9819 and an adjusted  $R^2$  value of 0.9585 at 95% confidence level. Besides that, this quadratic model is significant as proven by a high  $F$  value (42.10) and low  $P$  value (<0.0001).

The one factor plot on PS response is shown in Figure 3. For this response, the two main factors were the mass of TEA and temperature. As the amount of TEA increases, the PS decreases. In this reaction, TEA serves as a surface capping agent; thus, increasing it will increase its capability as a capping agent. Furthermore, TEA also promotes the formation of nuclei and the increase of the nucleus amount will produce smaller particles [11]. Besides that, larger particles were formed at higher temperature. One of the reasons for this observation is the domination of a particle growth process at high temperature [11, 22].

Based on ANOVA, SA and PS responses fitted into the linear and quadratic models, respectively. The linear model

does not have any interacting terms; thus, only the PS model has interacting terms and the terms that show significant interaction are  $X_2X_3$ . The 3D contour plots of the PS-combined mass of TEA and temperature as the parameters is shown in Figure 4. The maximum point (largest PS value) was observed when the mass of TEA and reaction temperature are the lowest and highest, respectively (0.06 g and 90°C). The minimum point occurred oppositely to the previous statement where the mass of TEA and temperature are the highest and lowest, respectively (0.20 g and 40°C). The results from this plot are consistent with the results discussed previously.

**3.2. Drug Loading and Drug Release Studies.** To evaluate the amount of drug loaded, the sample MSN-Q was analyzed using TGA and surface area and pore analysis. The TGA was done by comparing the weight loss that occurred for Q and MSN-Q. From Figure 5, it was shown that the complete mass loss of Q occurred at 400°C. Thus, in order to determine the amount of Q present in MSN-Q, the mass loss at 400°C was calculated and it was found that a total of 37% mass loss occurred at this temperature. It can be concluded that 37% of Q was successfully encapsulated in the MSN-Q which indicated high efficiency of rotary evaporation technique (75%), and this result is similar to the previous reports [18, 23]. MSN-Q was also analyzed using the surface area and pore analysis, and it was found that after the loading of drug, the surface area obtained a decrease from  $999.051 \text{ m}^2 \text{ g}^{-1}$  to  $432.267 \text{ m}^2 \text{ g}^{-1}$  and a decrease of pore volume from  $1.734 \text{ cm}^3 \text{ g}^{-1}$  to  $0.7962 \text{ cm}^3 \text{ g}^{-1}$ . This observation was expected as the pores of the silica filled with the drug which resulted in a lower surface area. Summary data of TGA is tabulated in Table 5.

The drug release studies were conducted using a dialysis bag with combined media of ethanol and PBS with a ratio of

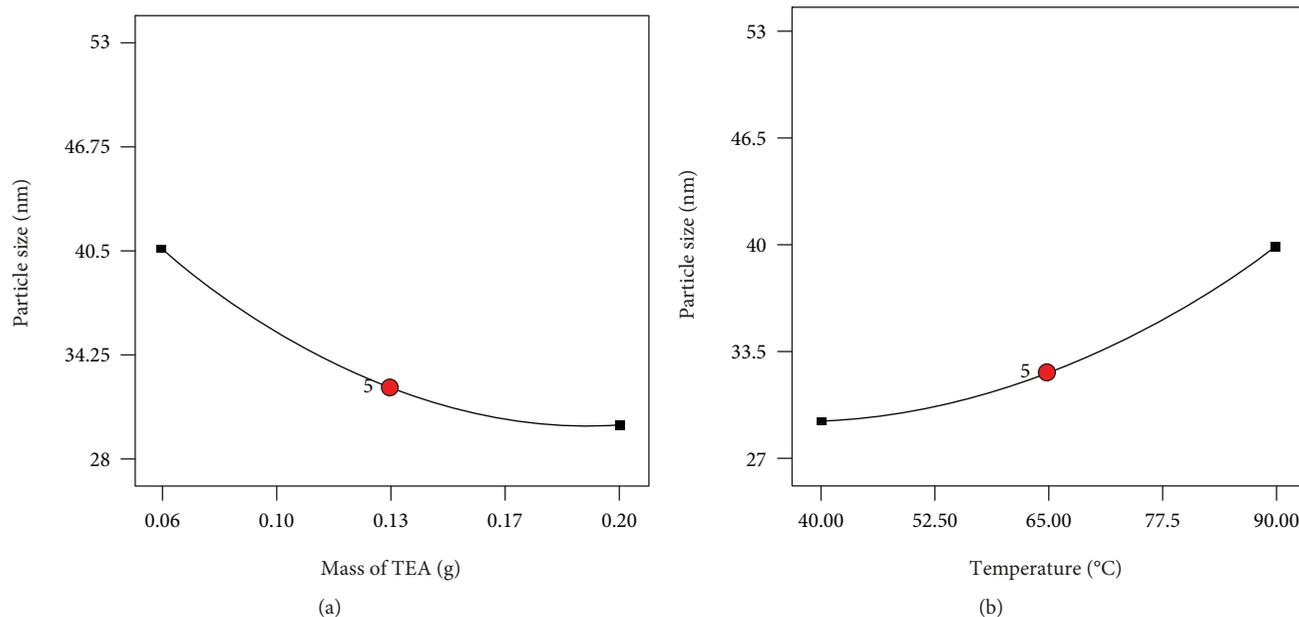


FIGURE 3: One factor plot for the (a) mass of TEA and (b) temperature on the PS.

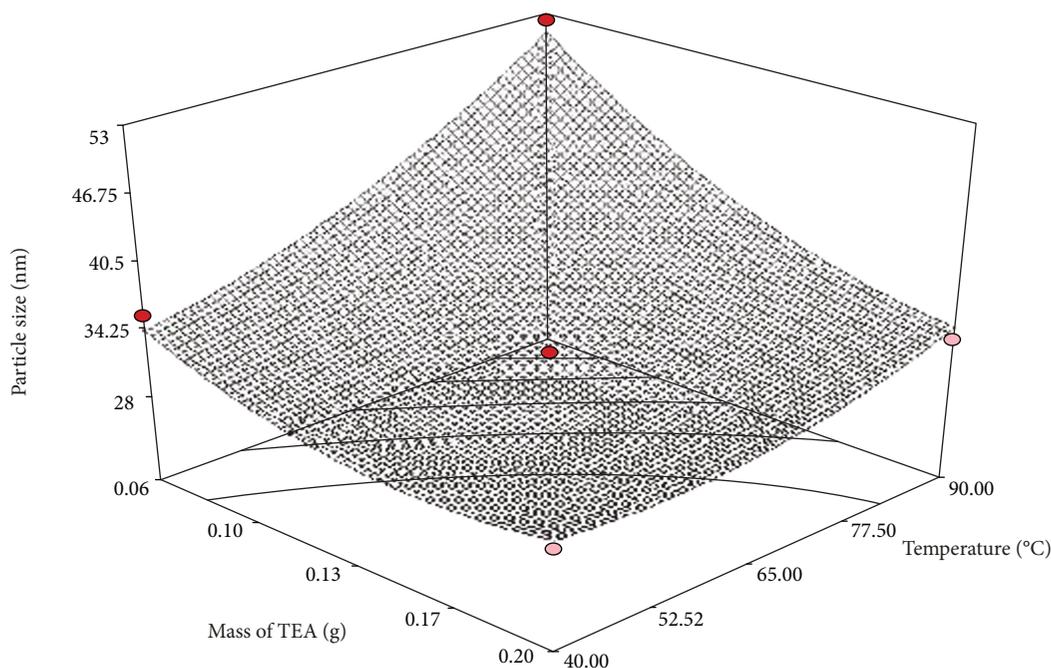


FIGURE 4: 3D plot for the interaction between two factors (mass of TEA and temperature) on the PS.

3:7. If only PBS was used as the media, there will be no drug present in the solution as the drug is insoluble in PBS. Therefore, a small amount of ethanol was required. The drug release studies were conducted using two samples which were Q and MSN-Q, and the experiments were run for 48 hours. It was found that the presence of MSN is able to increase the availability of the drug. This might be due to the change of crystallinity of quercetin to amorphous during the drug-loading process. Amorphous compound

is much more soluble thus increasing its bioavailability [24, 25]. From Figure 6, it was observed that after 48 hours, a cumulative release percentage of 6% and 32% was obtained for Q and MSN-Q, respectively. Furthermore, from the release profile, it takes 12 hours for MSN-Q to reach a stable release profile than Q which takes only 1 hour. This shows that with MSN, it is possible to have a slower release rate of drugs and increase its bioavailability at the same time [18, 26].

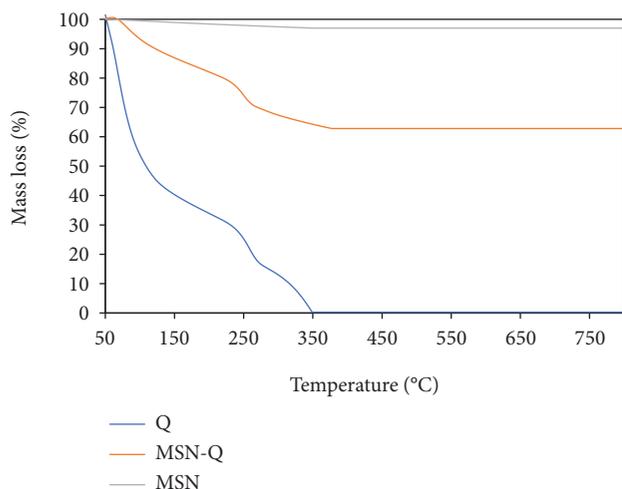


FIGURE 5: TGA curve of Q, MSN-Q, and MSN.

TABLE 5: Summary data from TGA.

Sample	Q	MSN-Q
Mass loss at 400°C (%)	100	37

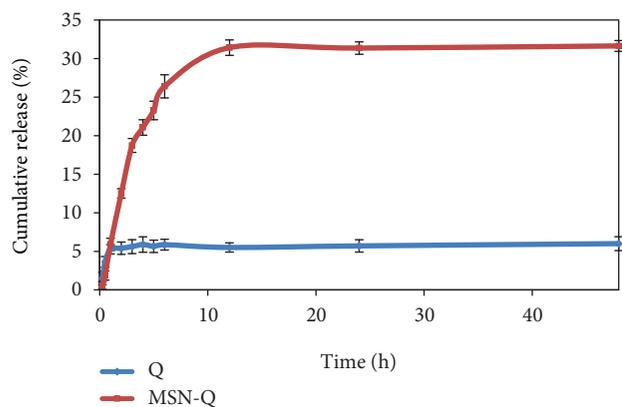


FIGURE 6: Drug release profile for Q and MSN-Q.

#### 4. Conclusion

The experimental design is a great tool to analyze and tune the properties of MSNs by three varied parameters which were the amount of template, TEA amount, and reaction temperature. The statistical analysis of the SA and PS indicates that the results show the best fit with the linear and quadratic models, respectively. Among these three variables, it was found that reaction temperature has the most significant impact on both the SA and PS. Based on the result obtained from the experimental design, MSN with the highest SA value was chosen for drug delivery studies. From the drug loading and drug release studies, it was found that a total of 37% of drug was successfully encapsulated in MSNs and 32% of the drug was released within 48 hours. This shows that the MSN has the potential to serve as a drug

delivery agent. Furthermore, the addition of functional groups attached to the MSNs may help to increase the percentage of drug load as well as produce a controllable drug release process.

#### Data Availability

The experimental data used to support the findings of this study are included within the article.

#### Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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