Journal of Research in Pharmacy

Research Article

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Silica nanoparticle synthesis by experimental design for drug and gene delivery applications

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Received: 29 May 2022 / Revised: 11 August 2022 / Accepted: 12 August 2022

ABSTRACT: Silica nanoparticles (SNPs) are one of the most researched drug/gene delivery platforms due to their easy and cheap production. Their toxicity depends on the nanoparticle characteristics like particle size or shape. It is well known that the smaller nanoparticles have a better cellular uptake potential. For this reason, in this study, we synthesized SNPs with a particle size of around 100 nm via an experimental design method that combines Technique for Order Preference by Similarity to the Ideal Solution (TOPSIS) with Taguchi design to optimize more than one response. After the optimization, average particle size, particle size distribution, zeta potential, and particle morphology of validated SNPs were analyzed. The cytotoxicity studies were performed on fibroblast cells (L929) for 48 and 72 hours. Results show that obtained nanoparticles were spherical-shaped with a size of around 100 nm and had good biocompatibility.

KEYWORDS: TOPSIS based Taguchi Design; design of experiment; silica nanoparticles; drug delivery; gene delivery

1. INTRODUCTION

Silica nanoparticles (SNPs) have a wide place in scientific research due to industrial applications such as pharmaceutical, electronics, catalysis, and thin-film substrates [1]. In 1968, Stöber, Fink, and Bohn developed a method [2] based on the hydrolysis reaction of silica alkoxides, $Si(OR)_4$ (where R is the radical group with the general formula C_mH_{2m+1}), forming siloxane (-Si-O-Si-) groups by hydrolysis and condensation which proposes the production of silica in micron (or submicron) sizes via a quite simple method [3]. However, controlling the size of SNPs depends on several factors such as the amount of reactant, the temperature of the system, and the mixing rate which requires optimization for each desired particle size. SNPs are good candidates for drug or gene delivery applications due to their biocompatibility, easy production, easily modified surface to gain a positive charge for gene delivery applications, and active targeting [4, 5]. Moreover, SNPs can be obtained in very small particle sizes. It should be remembered that keeping nanoparticle size around 100 nm is critical for cellular uptake efficiency and pathway [6-8]. In this study, we tried to develop an optimization method to obtain SNPs with small particle sizes.

Experimental design includes the methods used to determine the variables that can affect the process and suggests a set of experiments with varying amounts or proportions. Since the quality of the product is closely related to the features expected from the product, the features expected from the product should be revealed at the design stage [9]. Taguchi developed the experimental design method known as the Taguchi method, which is based on experimental design to improve quality. This method was created by combining partial factorial experimental design with concepts such as robust design and orthogonal arrays [10, 11]. In Taguchi's experimental design, the factors affecting the product's performance are divided into controllable and uncontrollable factors. The first of these are easily identifiable factors, but uncontrollable (noise) factors are the main causes of the variance.

How to cite this article: Ultav G, Tonbul H, Sahin A, Capan Y. Silica nanoparticle synthesis by experimental design for drug and gene delivery applications. J Res Pharm. 2023; 27(1): 12-22.

ISSN: 2630-6344

http://dx.doi.org/10.29228/jrp.243

Performance statistics is an evaluation method that compares different controllable factor levels and selects the most appropriate factor level combination. In the Taguchi method, the Signal/Noise (S/N) ratio is used as a performance statistic [12]. S/N can be expressed as the ratio of the mean to the standard deviation [13]. More reliable results can be obtained with this method than using the mean and standard deviation separately [14].

The S/N ratios developed according to the minimum, maximum, or best performance characteristics are given below [9, 15]. In these equations, "y" represents the performance characteristic value and "s^2" represents the variance.

In the case of minimum, y is required to be closest to zero and the related equation is given in Equation 1 (Eq 1).

$$\eta = -\mathbf{10}\,\mathbf{log_{10}}\left[\frac{1}{n}\sum_{i=1}^{n} y_i^2\right] \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \boldsymbol{Eq\ 1}$$

In the case of maximum, y is assumed to go to infinity and S/N will be as in Equation 2 (Eq 2).

$$\eta = -\mathbf{10}\,\mathbf{log_{10}}\left[\frac{1}{n}\sum_{i=1}^{n} \frac{1}{y_i^2}\right] \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \boldsymbol{Eq\ 2}$$

Target Value Best (product dimensions, electrical voltage, etc.). In such problems, for y a certain target value is given Equation 3 (Eq 3).

$$\eta = \mathbf{10}\,\mathbf{log_{10}}\left[\frac{\bar{y}^2}{s^2}\right] \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \boldsymbol{Eq\ 3}$$

The full factorial design brings a huge number of experiments when high numbers of factors and levels are required. This is a time-consuming and uneconomical approach. The Taguchi method avoids this situation with fractional factorial design; it reduces the number of experiments by using only orthogonal arrays and aims to provide maximum benefit from the minimum number of experiments. By using orthogonal arrays, all experiments are prevented from being tried one by one, and the number of experiments is reduced by changing more than one variable at the same time [16, 17].

Although it is possible to carry out optimization studies with a small number of experiments for a single response with the help of Taguchi design, it is not a suitable method for multi-response optimization. The Technique for Order Preference by Similarity to the Ideal Solution (TOPSIS) method is a frequently used method to classify in terms of closeness to the ideal solution. The method is based on choosing the one that is farthest from the negative ideal solution and closest to the ideal [18]. Criteria can be weighted according to their priority, also meaning that the most important criterion has the highest weight [18].
In this study, we studied SNPs with a particle size of around 100 nm to use them as a drug carriers or a gene delivery platform. This study suggests an approach to arranging conditions for SNP synthesis with preferred particle sizes. Particle size was weighted as 0.8 and particle size distribution was weighed as 0.2 due to the importance of particle size for a gene or drug delivery system. Making a multi-response optimization with TOPSIS combined Taguchi design can be an effective alternative. Moreover, besides the size measurements; zeta potential, SEM, and biocompatibility studies of optimized nanoparticles were conducted.

2. RESULTS AND DISCUSSION

The results obtained as a result of nine experiments according to the Taguchi experimental design obtained using orthogonal arrays are shown in Table 1.

Among the experimental results (responses) given above, the condition for the smallest particle size was determined by the "smaller is better" option of Minitab®. However, since the Taguchi design is not a method that provides optimization of more than one response at the same time, the responses were optimized one by one and the results were compared with the results obtained with the TOPSIS-based Taguchi design, which is a multi-response method.

http://dx.doi.org/10.29228/jrp.243
J Res Pharm 2023; 27(1): 12-22

Table 1. Responses by L_9 Taguchi Design

Experiment No	Uncoded Levels			Particle Size (nm)	Polydispersity Index
	A	B	C		
1	1	1	1	97,54	0,211
2	1	2	2	260,2	0,161
3	1	3	3	404,3	0,187
4	2	1	2	276,6	0,289
5	2	2	3	356,4	0,130
6	2	3	1	255	0,112
7	3	1	3	373,2	0,179
8	3	2	1	253,2	0,154
9	3	3	2	356,8	0,210

The calculations for the TOPSIS-based Taguchi design are shown in Table 2.

Table 2. Calculated S/N ratios for minimum particle size and polydispersity index by TOPSIS method and Minitab®

	Decision Matrix (S/N)			Normalized Decision Matrix (by weight)				
Exp no	R(PB) 0,8	R(PDI) 0,2		v(PB)	v(PDI)	Si+	Si-	Ci
1	-39,7837	13,5144		-0,2171	0,0592	0,0241	0,0684	0,7395
2	-48,3061	15,8635		-0,2636	0,0695	0,0485	0,0305	0,3863
3	-52,1341	14,5632		-0,2845	0,0638	0,0702	0,0166	0,1911
4	-48,8370	10,7820		-0,2665	0,0472	0,0612	0,0180	0,2272
5	-51,0388	17,7211		-0,2785	0,0777	0,0617	0,0310	0,3344
6	-48,1308	19,0156		-0,2626	0,0833	0,0455	0,0422	0,4808
7	-51,4388	14,9429		-0,2807	0,0655	0,0660	0,0186	0,2200
8	-48,0693	16,2496		-0,2623	0,0712	0,0468	0,0326	0,4109
9	-50,9972	12,5418		-0,2783	0,0550	0,0674	0,0099	0,1280
	146,6223[a]	45,6388[a]	A^+=	-0,2171	0,0833			
			A^-=	-0,2845	0,0473			

[a] The square root of the sum of the squares of each value in the column

The values indicated by Ci in Table 2 now represent the data obtained from this experimental design. In Table 2, A+ symbolizes the positive ideal solution and shows the best solution, in other words, the highest S/N ratio. A- symbolizes the negative ideal solution and shows the worst solution, in other words, the lowest S/N ratio. The distance of any experiments (i) to the positive or negative ideal solution was shown as Si+ or Si-, respectively. Ci is calculated deputy response which shows the similarity of the ideal solutions. This data (Ci column) was entered in response to the Minitab® program and it was understood that test run 1 should be used to obtain the smallest particle size and the lowest polydispersity particle. Related graphics was given in Figure 1.

http://dx.doi.org/10.29228/jrp.243
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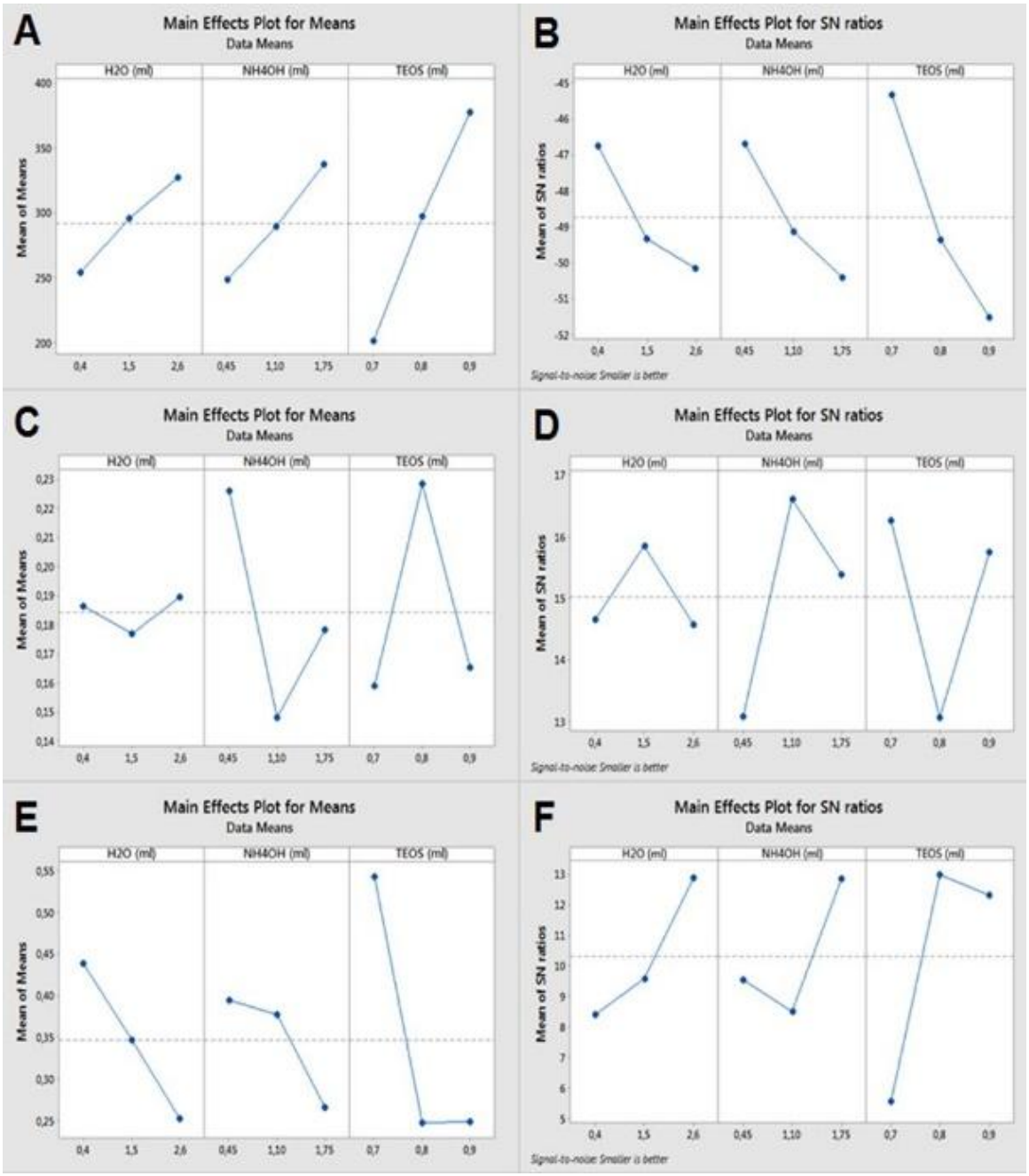

Figure 1. The main effect plots for the smallest particle size: A and B belong to the average particle size, and C and D belong to the optimization made according to the polydispersity index. E and F are obtained with TOPSIS-based Taguchi design.

After the experiments were performed, Taguchi Design analyzed each response. TOPSIS-based Taguchi solution was performed for two responses to see the difference. According to these results, for the minimum particle size, the minimum amount of TEOS and maximum amounts of NH_4OH and H_2O should be used while for minimum polydispersity minimum amount of NH_4OH is required. This means, that to reduce both responses a mutual solution is necessary. Figure 1 shows that optimizing particle size and polydispersity respectively gives different results which are not optimum for both responses.

The particle sizes and zeta potentials obtained as a result of the validation experiment of these particles are given in Figure 2.

http://dx.doi.org/10.29228/jrp.243
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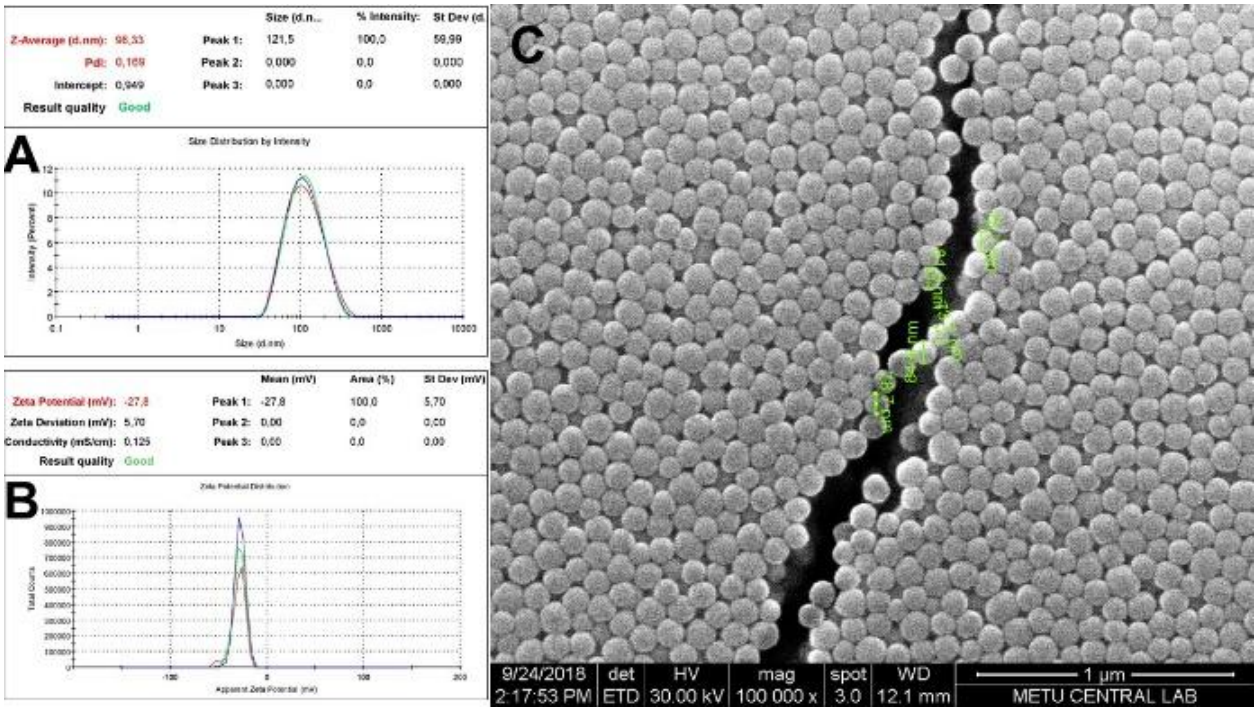

Figure 2. Results of validation: A B and C represent Particle size, zeta potential, and SEM image of optimum formulation respectively

After the determination of reaction conditions, the optimum conditions were performed for validation. According to the dynamic light scattering (DLS) result (Figure 2), particle size remained the same. The zeta potentials of the particles were also measured. Silica is negatively charged due to the -OH groups on its surface, and the results are consistent with this information. In addition, a zeta potential around -30 mV (-27 mV ±5.7) suggests that the stability of the particles in water is quite good. SEM image suggests that nanoparticles have a size of around 80 nm which complies with the DLS result measured at around 100 nm (98.33 nm ± 11.2) due to the hydrodynamic diameter included in DLS measurements.

These results indicated that the desired particle size was achieved at around 100 nm by applying the TOPSIS-based Taguchi design. The size of the nanoparticles is one of the key parameters in drug delivery systems to achieve optimal therapeutic outcomes. Pathophysiology of certain pathological conditions including cancer, inflammation, and wound healing often includes accelerated angiogenesis that may result in leaky vasculature and lack of lymphatic drainage [19]. This condition is a critical point for the establishment of the EPR effect and the size of the nanocarrier should reduce to benefit from the EPR effect. Moreover, the particle size of the nanocarrier also influences the particle-cell interaction and cellular internalization, and having a particle size under 100 nm is critical due to the activation of most cellular uptake mechanisms which means cellular uptake may increase with smaller particle sizes [20].

Apart from the effectiveness of the nanoparticle drug delivery system, the biocompatibility of the system should have also been considered. Furthermore, more attention should be paid to the toxicity of inorganic-based nanoparticles when compared to organic-based nanoparticles. SNPs are recognized as GRAS (generally recognized as safe) material by US FDA (United States Food and Drug Administration). Yet, EFSA (European Food Safety Authority) re-evaluates the toxicity of SNPs as food additives. There are numerous studies on toxicity evaluation and biocompatibility of SNPs as drug delivery systems. The general opinion on this subject is the biocompatibility of SNPs depends on the particle size, morphology, surface properties, and crystal structure of obtained nanoparticles [21-23]. Considering these features, non-toxic SNPs can be used as a drug delivery system with an optimized structure and the right dose. Therefore, in this study, we performed a cytotoxicity assay (MTT) to evaluate the effect of the SNPs on cells. For this purpose, we used mouse fibroblast cell line L929 which is also recommended by International Organization for Standardization (ISO) for biocompatibility studies. The obtained results were presented in Figure 3.

http://dx.doi.org/10.29228/jrp.243
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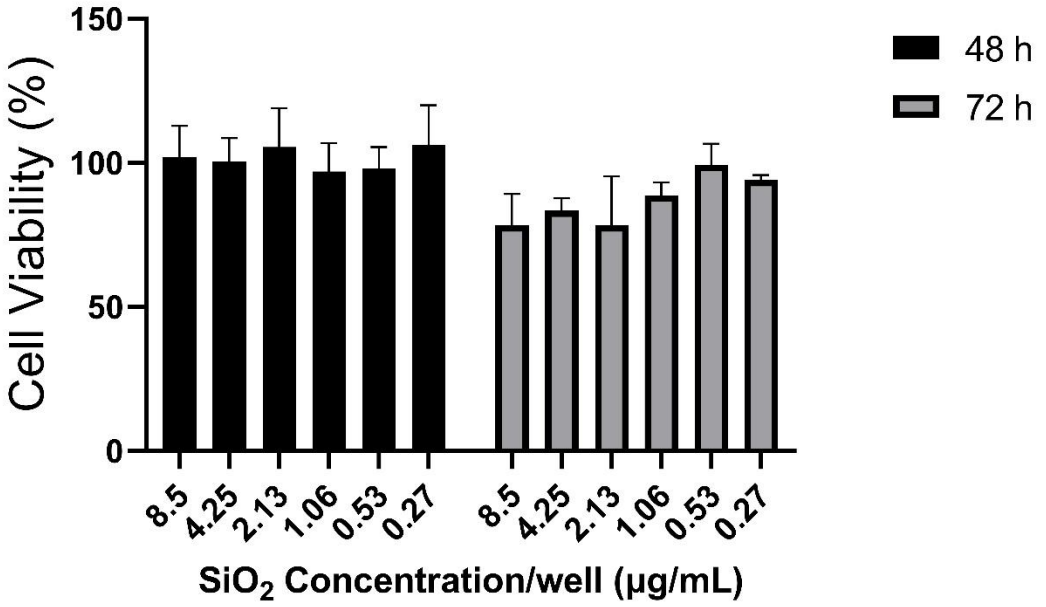

Figure 3. Cytotoxicity studies at L929 cell line at 48 and 72 h.

Generally, obtained results show that SNPs by the Stöber method are not toxic for the L929 cell line represented as Figure 3. No cell death was observed at any concentration at 48 h incubation time. Although cell death was observed at the 2.13, 4.25, and 8.5 µg/mL concentrations, cell viability was still around 80% at 72 h incubation time. According to these results, SNPs are not toxic for the L929 cell line and they are good candidates for drug or gene delivery.

SNPs are charged negatively as well as genes which means complexation cannot occur due to electrostatic repulsion between them. This can be achieved by surface modification of SNPs with some positively charged chemicals such as (3-Aminopropyl)triethoxysilane (APTES) and N-[3-(Trimethoxysilyl)propyl]ethylenediamine (TMSPE) [24]. Positively charged SNPs can carry genes due to positive-negative interaction. This strategy is beneficial also for drugs. Positively charged drugs can be carried by SNPs without any modifications, yet negatively charged ones may require a positive surface charge. Also, PEGylation of SNPs is quite simple which is important to exploit the shield-effect and prolong the blood circulation time [25]. In short, there are two strategies to achieve PEGylation of SNPs. The first one includes, after the positive charge creation on the surface by amine groups, using standard carbodiimide chemistry (NHS/EDC). The second one, suggests the usage of a PEG-Silane in aqueous media. Each surface modifications are easy to apply and has wide use in literature [26-29].

4. CONCLUSION

SNPs are promising drug and gene delivery platforms due to their good reproducibility and easy synthesis. In this study, SNPs were synthesized with a particle size of 100 nm by experimental design to obtain a drug/gene delivery platform candidate. An experimental design was performed and combined with a statistical approach to optimize 2 responses at a time. This approach minimizes the number of experiments to make research cost-effective and time-efficient. Then, these SNPs were characterized by DLS and SEM and both particle size and polydispersity index were chosen as responses. Optimized SNPs were found biocompatible according to cell culture results on the L929 cell line. In short, the obtained SNPs can be good candidates for drug delivery or gene carrier (with some surface modifications) applications due to their easy, fast, and cheap production or they can be used as template material for further nanoparticle synthesis.

http://dx.doi.org/10.29228/jrp.243
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5. MATERIALS AND METHODS

5.1. Materials

Tetraethyl orthosilicate (TEOS), ammonium hydroxide (NH_4OH, 33% w/w), sodium dodecyl sulfate, N, N-Dimethylformamide, and 3-(4,5-Dimethylthiazol-2-yl (MTT) were purchased from Sigma-Aldrich.

5.2. SNPs Synthesis Procedure

The Stöber method was used for the preparation of SNPs which is the most common synthesis method in the literature [2]. It was carried out by hydrolysis of TEOS in the presence of water and ammonia in an ethanol medium. The effects of the amounts of water, ammonia, and TEOS were investigated in this study to obtain a certain average particle size and distribution with the help of the experimental design matrix. The synthesis of amorphous silica is basically as follows:

1. Water and NH_4OH were added to ethanol and mixed for 15 minutes on a magnetic stirrer at room temperature.

2. TEOS was added to it quickly. After mixing for an hour SNPs were collected by centrifuge and washed before particle size and polydispersity analyses. For the DLS measurements, 100 µL particle solution was diluted to 2 ml with water.

5.3. TOPSIS Based Taguchi Design

The parameters affecting the particle size and polydispersity were determined as the concentrations of the components in the reaction medium. For this purpose, the amount of ethanol, which is the reaction medium, was kept constant at 10 mL. The amounts of TEOS, NH_4OH, and water were considered as factors affecting the particle size. Three levels were determined for each of these factors and their effects on the responses (particle size and polydispersity index). These levels were determined according to the literature[2, 30-33] and the Taguchi design is made with the help of Minitab®. The factors considered and their determined levels are shown in Table 3.

Table 3. Factors and levels of experimental design applied for the synthesis of amorphous silica as a template

Symbol	Factors	Levels		
		1	2	3
A	Silica precursor (TEOS) amount (mL)	0,7	0,8	0,9
B	Water (H_2O) amount (mL)	0,4	1,5	2,60
C	Ammonium hydroxide (NH_4OH) amount (mL)	0,45	1,10	1,75

In this study, Taguchi orthogonal array (L9) was used to evaluate the experimental results. Columns 3, 4, and 5 were given as levels in Table 3 showing the three control factors and their uncoded levels. This model enables three performance criteria to be used simultaneously in the analysis of factor effects. The design for carrying out the experiments is shown in Table 4.

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Table 4. Factors and Levels for silica synthesis

Experiment No.	Coded Levels			Uncoded Levels		
	A	B	C	TEOS amount (mL)	H_2O amount (mL)	NH_4OH amount (mL)
1	1	1	1	0,9	0,40	0,45
2	1	2	2	0,9	1,50	1,10
3	1	3	3	0,9	2,60	1,75
4	2	1	2	0,8	0,40	1,10
5	2	2	3	0,8	1,50	1,75
6	2	3	1	0,8	2,60	0,45
7	3	1	3	0,7	0,40	1,75
8	3	2	1	0,7	1,50	0,45
9	3	3	2	0,7	2,60	1,10

The obtained results from the Taguchi design were evaluated using the Taguchi design section of Minitab®.

5.4. Characterization of Nanoparticles

To calculate the obtained amount from synthesis, the obtained materials were dried in an oven and weighed (the process was repeated three times and the averages were taken).

Particle size and zeta potential measurements were analyzed with particle size and zeta potential measuring device (Malvern Zetasizer Nano series-ZS). After the particles were dispersed in water, three consecutive measurements were performed for each formulation at 25˚C and scattering angle of 173˚.

The morphology of optimized nanoparticles was investigated by Scanning Electron Microscopy (SEM) using Quanta 400F Field Emission. For this, a drop of diluted nanoparticle suspension in ethanol was dropped onto the grid, dried at room temperature, coated with gold-palladium, and then analyzed.

The biocompatibility of optimized nanoparticles was investigated in cell culture studies using the L929 cell line. After 2000 cells/well were seeded to 96 well-plate, it was kept at 37°C overnight and the next day SNPs suspended in RPMI with different concentrations were added to wells. Plates were kept at 37°C for 48 and 72 h and then an MTT assay was performed. Briefly, 25 µL MTT solution (5 mg/mL in PBS) was added to the wells and after 4 h, sodium dodecyl sulfate/ dimethylformamide solution was added to the wells to solve formed formazan crystals and set aside (dark) overnight. The plates were analyzed by an ELISA plate reader at 570 nm and evaluated by Student's T-test.

5.5. Proposed Methodology

L9 orthogonal array was selected to optimize particle size and polydispersity. The TOPSIS-based Taguchi method was performed to achieve optimization of two responses at a time. These two responses were determined as quality criteria and factors and their levels were selected according to the literature [2, 30]. The proposed 10-step methodology is summarized in Figure 4.

http://dx.doi.org/10.29228/jrp.243
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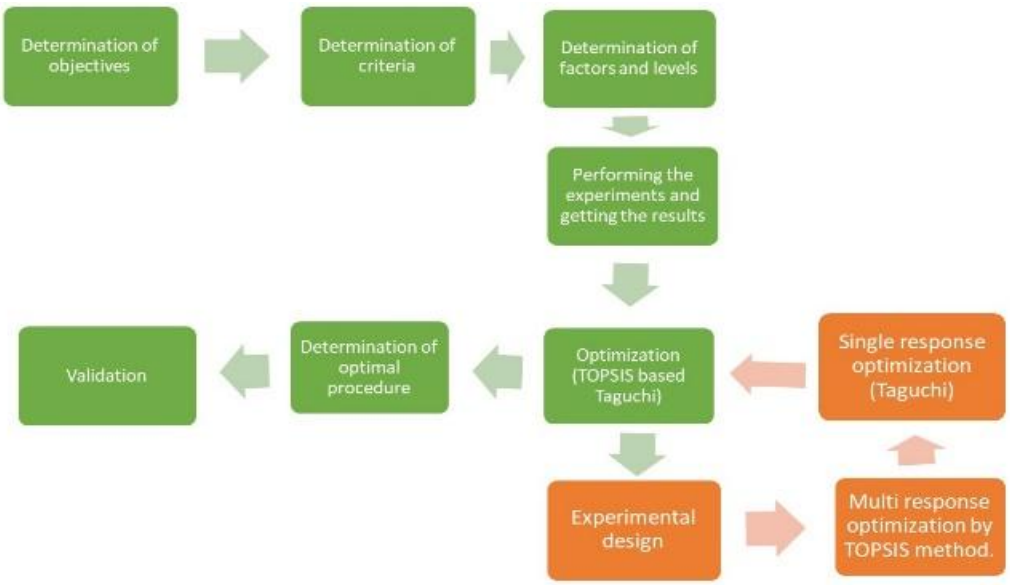

Figure 4. Proposed methodology

Acknowledgments: SEM was performed in Middle East Technical University Central Laboratory. A part of this study was supported by the Hacettepe University Coordinatorship of Scientific Research Projects with the project code THD-2016-12890. Special thanks to Esra Pezik for her support.

Author contributions: Concept – G.U.; Design – G.U.; Supervision – Y.Ç.; Resources – Y.Ç..; Materials – G.U., Y.Ç..; Data Collection and/or Processing – G.U., H.T.; Analysis and/or Interpretation – G.U., H.Y., A.Ş..; Literature Search – G.U., H.T.; Writing – G.U.; Critical Reviews – G.U., H.T.

Conflict of interest statement: The authors declare no conflict of interest.

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