

Development, characterization, and *in vitro* dissolution of self-nanoemulsifying drug delivery system (SNEDDS) for an effective oral delivery of quercetin

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ABSTRACT: Quercetin has been known to have antimicrobial activity. The low solubility causes the bioavailability of quercetin to be reduced, reducing its effectiveness of quercetin. Self-nanoemulsifying drug delivery system (SNEDDS) is able to be used to increase the bioavailability of quercetin. The purposes of this study were to investigate the optimum SNEDDS components' concentration, namely the oil, cosurfactant, and surfactant which produce SNEDDS with good characteristics, and to determine the dissolution of quercetin SNEDDS preparations. Optimization of the components that make up SNEDDS is done by applying the method of simplex lattice design using the Design Expert software. Quercetin SNEDDS was characterized by testing the transmittance percentage, time of emulsification, average droplet size, polydispersity index, zeta potential, and validated in vitro dissolution. The upper and lower borders of the SNEDDS component concentrations selected for oleic acid, polysorbate 80, and polyethylene glycol 400 respectively were 10-20%, 70-80%, and 10-20%. The optimum formula for SNEDDS contained oleic acid, polysorbate 80, and PEG400 of 10%, 73.2%, and 16.8%, respectively. The transmittance percentage, average droplet size, polydispersity index, and zeta potential values were 89.97±3.31; 116.20±0.44; 0.25±0.06; and -30.47±0.12. The results of in vitro dissolution illustrated that the percentage of dissolution value of quercetin SNEDDS was superior to that of plain quercetin ($p < 0.05$). Quercetin SNEDDS with good characteristics has the potential to be developed as a quercetin delivery system with high drug bioavailability.

KEYWORDS: Quercetin; SNEDDS; Optimization; Characterization; Dissolution.

1. INTRODUCTION

Quercetin (Qc), with the IUPAC name of 3,3',4',5,7-pentahydroxyflavone is a dietary flavonoid that is generally contained in apples, berries, onions, seeds, nuts, flowers, barks, vegetables, tea, and leaves. Several studies reported that Qc possessed anti-carcinogenic, anti-diabetic, anti-ulcer, anti-inflammatory, anti-viral, and anti-allergic activities [1]. Furthermore, several studies reported that Qc also indicated an antimicrobial activity that can be beneficial for the development of antibiotics [2-4]. Showing various advantageous activities, Qc delivery throughout the body faces the main obstacle, which is low oral bioavailability due to the low aqueous solubility of Qc [5]. In order to provide a satisfying Qc delivery, innovation in the formulation method is needed.

The utilization of nanotechnology in drug formulation yields numerous advantages, particularly in increasing the solubility of drugs. SNEDDS (self-nanoemulsifying drug delivery system) is one kind of nanoparticle formulation that can be implemented in raising the efficacy of the Qc that is administered orally. SNEDDS is a lipid base nanoparticle formulation possessing an isotropic composition of oil, surfactant, and cosurfactant. Specifically, having contact with the water phase, SNEDDS will form an emulsion with a particle size of below 200 nm [6]. Moreover, the nano-scale particles yield an improvement in Qc solubility and further escalate the drug bioavailability [7].

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In the strive of gaining the optimum formula of Qc-SNEDDS, an efficient optimization method is needed. The method of trial and error is no longer favored as it showed some disadvantages, such as time-consuming, high cost needed, and the high risk of optimization failure [8]. Therefore, the use of experimental design in the optimization of dosage form formulas is significantly increasing [9,10]. Simplex lattice design (SLD) is one of the experimental design methods in which the sum of the independent variables is set to be constant. This method is considered suitable to be implemented in the strive of finding an optimum condition of the formula's ingredients [6,11,12]. There were other studies that conducted formulation of Qc in several forms of nanoformulations with the main purpose of improving Qc's solubility as done in the present study [5,7,13,14]. However, as far as our knowledge, there were no studies that involved the optimization of Qc formulation using an experimental design that had been done before. Thus, the present study was done by utilizing the advantage of the SLD method in order to obtain an optimum formula of Qc-SNEDDS.

The purposes of this study were to determine the Qc-SNEDDS optimum formula using the SLD method with 3 factors and 2 levels. The three factors used were the concentration of SNEDDS components, which were oil, surfactant, and co-surfactant. Subsequently, the Qc-SNEDDS optimum formula was tested for its in vitro dissolution in order to observe whether the SNEDDS dosage form successfully increased the solubility of Qc.

2. RESULTS

2.1. Solubility study of Qc

The yielded Qc solubility data are presented in Figure 1, which indicated that P80 and PEG400 are the SNEDDS component that can solubilize Qc in the highest amount among the other components. Moreover, the higher amount of Qc dissolved in OA compared to water indicated the suitability of Qc to be manufactured in the form of oil-in-water nanoemulsions.

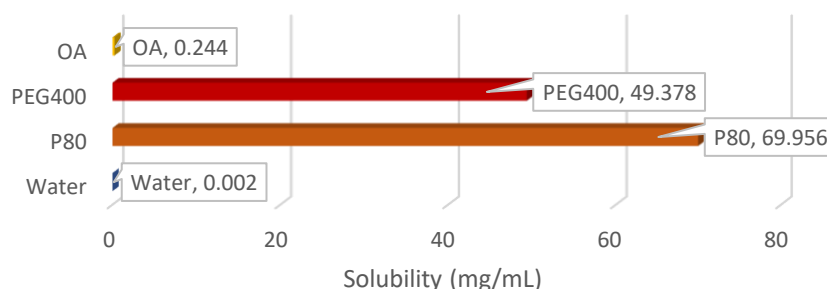


Figure 1. The solubility of Qc in the SNEDDS components.

2.2. Pseudo-ternary phase diagram

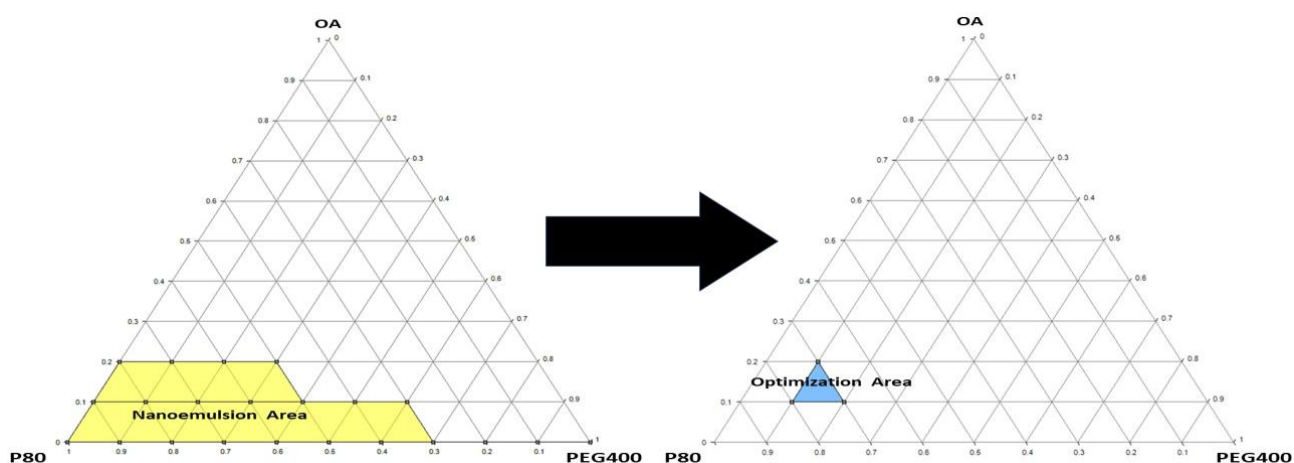


Figure 2. The pseudo-ternary phase diagram depicting the nanoemulsion area and the selected area to be further used as the optimization area.

The development of pseudo-ternary phase diagram yielded the area with clear visibility of the formed emulsions. This transparent appearance area (OA of 0-20%, P80 of 30-100%, and PEG400 of 0-70%) was assumed as the region in which nanoemulsions were formed. The area was shrunk into a smaller area for optimization using SLD. The pseudo-ternary phase diagrams indicating the formed nanoemulsion area and optimization area are presented in Figure 2.

2.3. Formula optimization

Based on the studies of the diagram of pseudo-ternary phase, the upper and lower borders of OA, P80, and PEG400 were 10-20%, 70-80%, and 10-20%, respectively. The formulation runs used in SLD were presented in Table 1 with the range of emulsification time and transmittance percentage were 15-118 seconds and 49.6-93.4%, respectively. Furthermore, the statistical parameters of all of the responses were provided in Table 2.

Table 1. The design of optimization of Qc-SNEDDS using SLD.

Runs	OA (%) (X ₁)	P80 (%) (X ₂)	PEG400 (%) (X ₃)	Emulsification Time (second) (Y ₁)	Transmittance (%) (Y ₂)
1	20	70	10	115	49.6
2	10	80	10	36	65.7
3	10	70	20	18	87.3
4	13	74	13	51	62.1
5	15	75	10	85	62.8
6	10	75	15	15	93.4
7	15	70	15	62	68.3
8	10	80	10	38	65.7
9	12	76	12	43	80.6
10	12	72	16	49	67.1
11	10	70	20	19	87.4
12	20	70	10	118	49.6
13	16	72	12	95	58.1

Table 2. The statistical parameters of the responses.

Parameters	Emulsification Time (Y ₁)	Transmittance (Y ₂)
Model p-value	0.0009	<0.0001
Mean	57.23	69.05
SD	6.02	0.85
CV	10.51	1.23
R ²	0.9905	0.9988
Adequate precision	20.033	61.981
Regression equation	$Y_1 = 116.91 X_1 + 37.41 X_2 + 18.91 X_3 + 37.95 X_1X_2 - 17.05 X_1X_3 - 46.05 X_2X_3$	$Y_2 = 49.66 X_1 + 65.76 X_2 + 87.41 X_3 + 21.32 X_1X_2 + 0.019 X_1X_3 + 68.22 X_2X_3$

2.4. The prediction and verification of the optimum formula

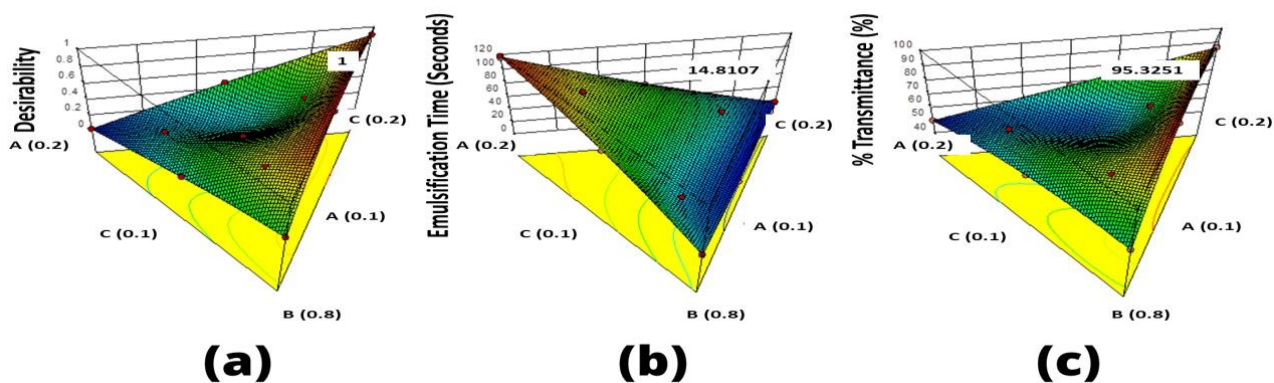


Figure 3. 3D surface plot of desirability (a), emulsification time (b), and transmittance (c).

Based on the consideration of several formula ingredients suggested by the SLD, the selected conditions for the optimum formula were 10% of OA, 73.20% of P80, and 16.80% of PEG400. Figure 3 illustrates the predictions of desirability (1.000) in the red region, emulsification time (14.81 seconds) in the blue region, and transmittance percentage (95.32%) in the red region. The statistical analysis indicated a significant difference between the predicted and observed values of emulsification time (28.88 ± 0.79 seconds) ($p < 0.05$), while no significant difference ($p > 0.05$) in the transmittance ($89.96 \pm 3.30\%$).

2.5. Globule size, polydispersity index, zeta potential, and surface morphology

The results of Qc-SNEDDS characterization were provided in Table 3, in which the obtained globule size was smaller than 200 nm, the polydispersity index was below 0.7, and the zeta potential surpassed -30 mV. The morphology of dispersed particles of Qc-SNEDDS is depicted in Figure 4. The result of the TEM study indicated that the particles dispersed in the nanoemulsion were well dispersed in the spherical forms with the absence of aggregation.

Table 3. The results of Qc-SNEDDS characterization (n = 3).

Parameters	Results
Average globule size	116.20 ± 0.40 nm
Polydispersity index	0.247 ± 0.05
Zeta potential	-30.40 ± 0.11 mV

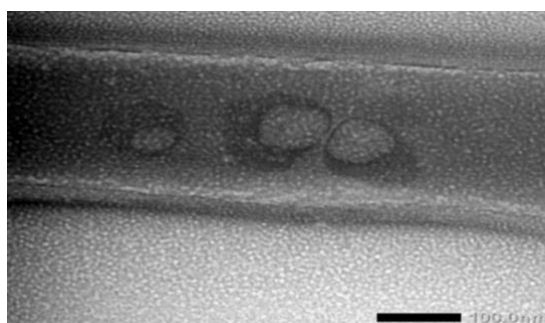


Figure 4. The result of transmission electron microscopy (TEM) study of Qc-SNEDDS.

2.6. In vitro dissolution studies

In the in vitro drug dissolution studies, the cumulative Qc dissolution in the form of SNEDDS was higher than the plain formulation of Qc in both dissolution media ($p < 0.05$). Moreover, there was no difference statistically ($p > 0.05$) between the cumulative Qc-SNEDDS dissolution in the media of SIF with the pH of 1.2 and in the media of SGF with the pH of 6.8. The results of the in vitro dissolution studies are presented in Figure 5.

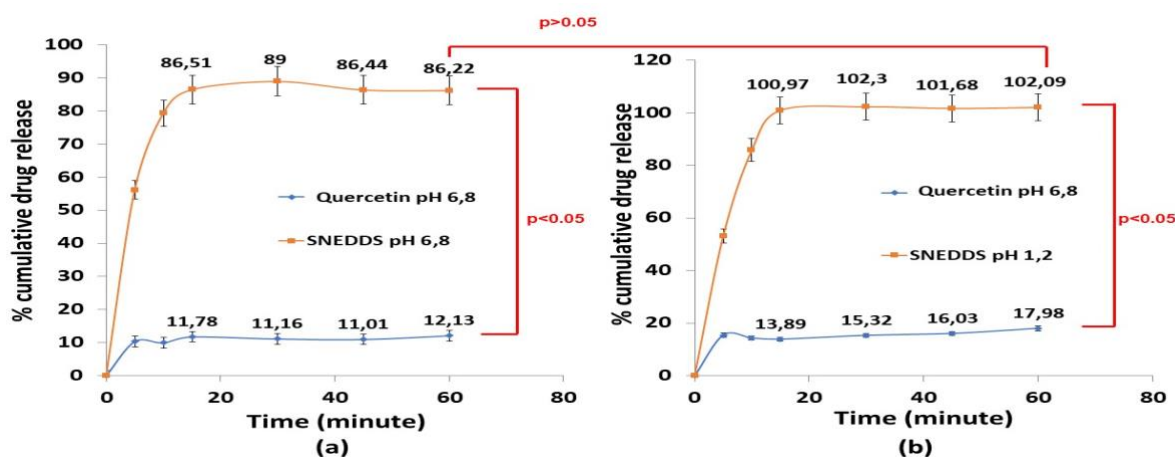


Figure 5. Qc-SNEDDS dissolution (orange line) compared to the plain Qc dissolution (blue line) in the media of SIF with pH of 6.8 (a) and SGF with pH of 1.2 (b) (n = 3).

3. DISCUSSION

The solubility study showed that Qc-SNEDDS can form the system of oil in water nanoemulsion, as the Qc was dissolved in a higher amount in OA compared to water. Although the lack of type of oils, surfactants, and cosurfactants explored in the present study, the selection of OA, P80, and PEG400 as the SNEDDS constituents was supported by another study that illustrated the highest solubility of Qc on those materials compared to the other tested ingredients [7]. Besides the solubility study results, the pseudo-ternary phase diagram, which was used in determining the range of SNEDDS components concentration that yielded nanoemulsion formation, was also able to be used in predicting the suitable nanoemulsion system [15]. Moreover, the formed pseudo-ternary phase diagram indicated that the oil in water system was suitable for Qc, as the transparent visuals were formed in the area with the low percentage of the oil phase [16]. P80 and PEG400 are suitable to be utilized as the surfactant and co-surfactant of Qc-SNEDDS, as they will be absorbed in the interface of oil and water, thus lowering the interfacial energy and preventing the coalescence condition to occur. This will increase the thermodynamic stability of nanoemulsion formed from the contact of Qc-SNEDDS with water. Furthermore, PEG400 as the co-surfactant can infiltrate the surfactant film, thus provide slots in between the surfactant's molecules, which eventually increasing the interfacial fluidity [17].

The optimization study using SLD indicated significant effects of the factors against emulsification time and transmittance. The statistical parameters, such as the R² values of higher than 0.7, and the values of adequate precision of above 4.0 illustrated that the used SLD model can explain the correlation between the concentrations of OA, P80, and PEG400 with emulsification time and transmittance [9,18]. The desirability value of 1.000 illustrated the possibility of the model to yield a precise prediction of the actual values of emulsification time and transmittance percentage. The actual value of transmittance percentage of Qc-SNEDDS optimum formula depicted the high transparency of the formed nanoemulsion, as the value was closer to 100%. Meanwhile, the actual result of emulsification time was significantly different from the predicted value. However, the obtained real emulsification time is still considered an acceptable value [19-21].

The size of the dispersed particles in nanoemulsion is a decisive aspect in the pace and amount of Qc's dissolution and absorption in the gastrointestinal tracts. The smaller particle can easily dissolve and subsequently diffuse in the digestive system. More specifically, the smaller globule size means the wider effective surface area to allow an increase in the Qc's absorption process [22]. The polydispersity index illustrates the uniformity level of the dispersed globules, in which a value of lower than 0.7 is expected as it depicts a uniform particle distribution. The polydispersity index of 0.247 ± 0.05 possessed by the Qc-SNEDDS will circumvent the condition of Ostwald ripening, which is the condition of coalescence that take place due to a significant difference of size in the dispersed particles. In the situation of Ostwald ripening, the smaller particle will permanently incorporate into the larger particles yielding the formation of significantly bigger particle size. Ultimately, this phenomenon will lead to an unstable form of nanoemulsion [23,24]. Zeta potential values shows the condition of surface charge of dispersed particles in nanoemulsions. A value of more than positive or negative 20 mV is preferred. The zeta potential of Qc-SNEDDS of -30.40 ± 0.11 mV will form a high repulsion force between the dispersed globules and eventually hinder the merge of particles [12,20]. Eventually, the result of TEM studies confirmed the size and shape of the dispersed particles of Qc-SNEDDS. The shape of particles played a role in dissolution, in which the spherical-shaped particles tend to be dissolved faster than the non-spherical globules [25].

The dissolution studies indicate the Qc's solubility in the media of dissolution that represents the condition of drug dissolution in the digestive system. The results of in vitro dissolution study in both dissolution media illustrated the successful solubility improvement of Qc due to the formulation of SNEDDS, as the cumulative Qc dissolutions in the SNEDDS form were significantly higher than in the plain formula of Qc. In SNEDDS dosage forms, the formation of very low emulsions needs the presence of free energy, which allow the formation of the oil-water interface spontaneously. The formation causes a significant dwindle of particle size and simultaneously improves drug release [22,26]. The results of in vitro dissolution experiments in the present study were in accordance with several other studies that formulated Qc in the form of nanoformulation. Kakran et al found that Qc in the form of nanosuspension dosage forms showed a superior dissolution percentage compared to plain Qc, while Fujimori et al proved that the Qc in the form of aggregated nanostructures significantly increased the amount of Qc dissolved compared to Qc crystals and physical mixtures of Qc and Rutin, indicating the advantageous ability of nano-scale drugs [13,14]. However, although its prominent results, the dissolution experiments conducted in the present study need to be further

investigated to determine the release of Qc from the nanoparticulate system. One of the methods that can be carried on is the dialysis technique combined with the USP dissolution apparatus [5,27]. Moreover, further study is needed in order to determine the bioavailability of Qc formulated as a SNEDDS dosage form.

4. CONCLUSION

The development of Qc-SNEDDS has been successfully done with sufficient characteristics of emulsification time, percentage of transmittance, average globule size, polydispersity index, zeta potential, and surface morphology. More importantly, the QC-SNEDDS possessed the ability to dissolve Qc in a significantly higher amount compared to the plain Qc. However, pharmacokinetic studies will be further needed to ensure that the bioavailability of Qc can be improved by SNEDDS formulation.

5. MATERIALS AND METHODS

5.1. Materials

Quercetin (Qc) (Shaanxi Yuantai Biological Technology Co., Ltd, China); oleic acid (OA) (Merck, USA); polysorbate 80 (P80) (Kao Indonesia Chemical, Karawang, Indonesia); polyethylene glycol 400 (PEG400) (Petronas Chemical, Malaysia); ethanol pro analysis, potassium dihydrogen phosphate, sodium hydroxide, potassium chloride (Merck, USA); hydrochloric acid (Smart Lab, Indonesia).

5.2. Solubility study

The Qc's solubility test in the present study was conducted using a validated method which consisted of the investigation to linearity, limit of detection, limit of quantification, accuracy, and precision parameters [28]. Initially, Qc in an excess mass was poured to four tubes in which each tube was added with 5 ml of OA, P80, PEG400, and water, respectively. Moreover, each tube was stirred for 24 hours to reach an equilibrium state. Furthermore, all of the tubes were centrifuged for 15 minutes with a velocity of 3000 rpm. Eventually, the supernatants were separated and analyzed using UV-Vis Spectrophotometer (Shimadzu UV-1800) at the wavelength of 373 nm using ethanol pro analysis as the blank [12].

5.3. Pseudo-ternary phase diagram construction

The pseudo-ternary phase diagram (ProSim Ternary Diagram 1.0) was created in order to obtain the range of each SNEDDS component that yields a transparent visual of nanoemulsion. OA, P80, and PEG400 were mixed into 66 mixtures representing each dot in the diagram (Figure 6). The region that produces transparent visuality was further used in the consideration of the lower and upper limits of each SNEDDS component in the optimization study [11].

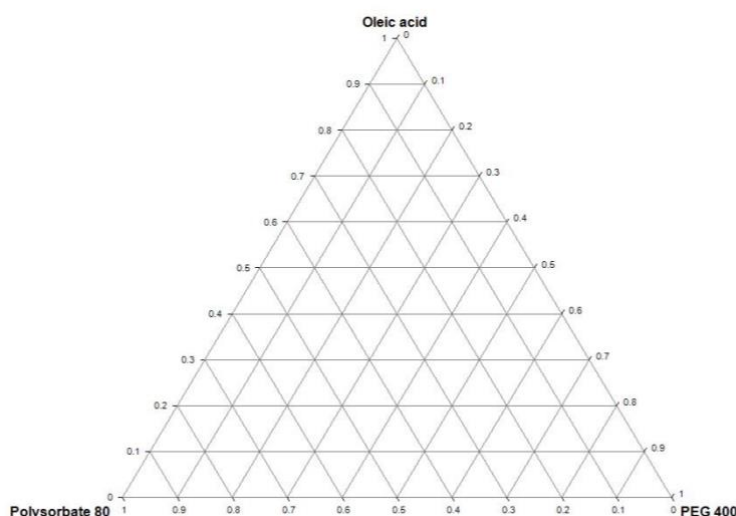


Figure 6. Pseudo-ternary phase diagram consisting of OA, P80, and PEG400.

5.3. Formula optimization

The optimization of Qc-SNEDDS was conducted using the SLD method with Design Expert software (Stat Ease Inc., USA). The concentrations of OA (X1), P80 (X2), and PEG400 (X3) were used as the factors. The considered responses were emulsification time (Y1) and transmittance percentage (Y2).

Qc-SNEDDS was prepared by carefully weighing 90 mg of Qc, and then sequentially added with a certain amount of OA, PEG400, and P80, respectively, with the final QC-SNEDDS volume of 3 ml. Moreover, the Qc-SNEDDS emulsification time was observed by dropping the Qc-SNEDDS with the volume of 1 ml into 100 ml of water phase and was subsequently stirred at the velocity of 200 rpm. The time required for the Qc-SNEDDS to totally dissolve with water was measured. Furthermore, the completely-dissolved SNEDDS was subjected to the transmittance percentage test by employing a UV-Vis Spectrophotometer (Shimadzu UV-1800) at 650 nm using the double-distilled water as the blank solution [6,22].

The prediction of the optimum Qc-SNEDDS formula was conducted by observing several aspects in the Design Expert software. Furthermore, the selected optimum formula was verified by using the one-sample t-test [9].

5.4. The analysis of droplet size, polydispersity index, zeta potential, and surface morphology

The measurements of droplet size, polydispersity index, and zeta potential were conducted by employing the particle size analyzer (Horiba SZ-100). A milliliter of diluted Qc-SNEDDS was poured into the test cuvettes and analysed in triplicates. Furthermore, the examination of the dispersed droplet's surface morphology was done by using transmission electron microscopy (TEM) (JEOL JEM-1400) [29].

5.5. In vitro dissolution test

The in vitro dissolution of Qc-SNEDDS was done by using a validated method and the instrument of the USP dissolution apparatus I (Electrolab, India). The validation results were presented in another publication and conducted by assessing the parameters of linearity, the limit of detection, limit of quantification, accuracy, and precision [28]. The conditions of rotation speed and temperature of the studies were 100 rpm and $37\pm 0.5^{\circ}\text{C}$, respectively. The simulated gastric fluid (SGF) with the pH of 1.2 and the simulated intestinal fluid (SIF) with the pH of 6.8, both without enzymes, were separately used as the dissolution media in the volume of 900 ml. Qc-SNEDDS containing the amount of Qc of 30 mg was packed into hard gelatin capsules and immersed in the flask of dissolution filled with the media. The volume of 5 ml of aliquots (5 ml) were obtained in the intervals of 5, 10, 15, 30, 45, and 60 minutes, and were subsequently replaced with the fresh media with the equal volume as the previously withdrawn. The collected samples were analysed with UV-Vis Spectrophotometer (Shimadzu UV-1800) at 366 nm and 369 nm for SGF and SIF, respectively. The cumulative drug dissolution was measured and compared to the formulation of plain Qc [22].

5.6. Statistical analysis

The optimization studies were analysed using ANOVA in order to inspect the effects of the independent variables against the dependent variables. Moreover, the obtained optimum formula was verified using the statistical method of one-sample t-test. Furthermore, the results of the optimum formula characterization were depicted as mean \pm standard deviation. Finally, the dissolution studies of Qc-SNEDDS were analysed by using a two-sample t-test.

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Conflict of interest statement: All authors declare that there is no conflict of interest associated with the study presented in this manuscript.

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