RESEARCH ARTICLE

Response Surface Methodology as a Tool for Optimization of self-nanoemulsified Drug Delivery System of Quetiapine Fumarate

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Abstract

Aim: The objective of the present study was to design self nanoemulsifying drug delivery system of quetiapine fumarate by optimizing particle size, zeta potential, and drug release using response surface methodology. **Materials and Methods:** Self-nanoemulsified drug delivery system formulations were prepared using Labrafac Lipophile WL as oil, Tween 80 as a surfactant, and Capryol 90 as a cosurfactant. Pseudo-ternary phase diagrams of oil, surfactant/co surfactant, and water were developed using the water titration method. Different Smix ratios were prepared, and the maximum ratio was selected for self-nanoemulsified drug delivery system (SNEDDS) formulation. D-optimal design for 3 factors at 3 levels each was employed systematically to optimize particle size, zeta potential, and drug release. **Result and Discussion:** The polynomial mathematical model generated for response and found to be significant. The optimized model predicted a particle size 54.42 nm, zeta potential −13.03 mv, and drug release 93.67% residual plots for particle size, zeta potential, and % drug release indicates points nearly closed to straight lines indicating good model. The signal-to-noise ratio effect was studied which causes r^2 value closer to 0.5. **Conclusion:** The quantitative effect of these factors at different levels was predicted using polynomial equation. Response methodology was then used to predict the levels of the factors A, B, and C required to obtaining an optimum formulation. A new formulation was prepared according to these levels. Signal-to-noise ratio was studied. Observed response was in close agreement with the predicted values of the optimized formulation, thereby demonstrating the feasibility of the optimization procedure in developing SNEDDS of quetiapine fumarate.

Key words: Response surface methodology, self-nanoemulsified drug delivery system, quetiapine fumarate

INTRODUCTION

Oral route has been the major preferred route of drug delivery for the chronic treatment of many diseases, due to convenience and improved patient safety, but approximately 35-40% of new drug candidates have poor aqueous solubility. The oral drug delivery of such drugs is frequently associated with low bioavailability, high inter and intrasubject variability, and lack of dose proportionality.[1,2] Efforts are needed to enhance the oral bioavailability in the gastrointestinal (GI) tract. Currently, numerous methods utilized for drug solubility enhancement including solid dispersion, liposomes, polymer micelles, nanoemulsions, cyclodextrin inclusion, and self-emulsifying drug delivery system (SEDDS) are adopted to develop the oral drug delivery system because of their stability and possibility of easy oral administration to improve drug self-emulsification in the gut.

Self-nanoemulsifying systems are isotropic mixtures of natural or synthetic oils with lipophilic or hydrophilic surfactants which undergo spontaneously emulsification when exposed to the GI fluids to form o/w nanoemulsion.[3] Rapid emulsification of these systems under mild agitation *in vivo* generates high surface area, and thereby, increases the

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rate and extent of absorption and results in more reproducible blood time profiles.[4] In addition, lymphatic uptake of the drugs is enhanced due to the small globule size and surface charge associated with it.[5] Therefore, particle size, drug release and zeta potential were selected as optimization criteria.

However, such formulations, in general, are developed on trial and error approach of changing one variable at a time. By this conventional approach, it is possible to develop the formulation with specific characteristics; however, it is difficult to get the true optimum composition.[6] This methodology requires a large number of experiments to select excipients and also to analyze the effect of excipients on the formulations characteristics.

The statistical optimization design has been documented for the formulation of pharmaceutical solid dosage forms. Here, self-nanoemulsified drug delivery system (SNEDDS) was tried to optimize on the basis of particle size after dilution in double-distilled water which is profoundly influenced by several formulation variables. In the development of a SNEDDS, an important consideration is to design an optimized formulation with an appropriate particle size, zeta potential, and drug release, with a minimum number of trials. Statistical experimental design methodologies are powerful, efficient, and systematic tools in the design of pharmaceutical dosage forms, allowing rational study of the influence on formulation and/or processing parameters on the selected responses with a shortening of the experiment work. The main objective of the experimental design strategies is to plan experiments to obtain the maximum information regarding the considered experimental domain with the lowest numbers of experiments. Many statistical designs have been recognized as useful techniques to optimize the process variables. For this purpose, a computer-based optimization technique with a response surface methodology (RSM) utilizing a polynomial equation has been widely used. Different types of RSM design include 3level factorial design, central composite design, Box–Behnken design, and D-Optimal design. In RSM only a few significant factors are involved in optimization. The technique requires minimum experimentation and time, thus proving to be far more effective and cost-effective than conventional methods of formulating SNEDDS.[7,8]

As a type of quality by design, RSM is generally applied to experimental situations where several independent variables influence a response variable.

Quetiapine fumarate is a psychotropic agent belonging to a chemical class of dibenzothiazepine derivatives. It is a white or almost white powder, moderately soluble in water. Quetiapine fumarate is a BCS class II drug. It is reported to have very low oral bioavailability (9%). The half-life is only 6 h.[9] It is used to treat psychosis associated with Parkinson's disease and chronic schizophrenia. The antagonist activity of quetiapine fumarate at dopamine and serotonin receptors is mediated the antipsychotic effect. Quetiapine fumarate has also an antagonistic effect on the histamine H1 receptor. This is thought to be responsible for the sedative effect of the drug. It is used to treat psychosis associated with Parkinson's disease and chronic schizophrenia. These antipsychotics have a low incidence of extrapyramidal side effects and tardive dyskinesias compared to older antipsychotics.[9-11]

Quetiapine fumarate is well absorbed and extensively metabolized following oral administration. The half-life is only 6 h. Quetiapine fumarate is approximately 83% bound to plasma proteins. Quetiapine fumarate is a weak acid with a dissociation constant (pK_a)3.3 and 6.8 with moderate pH-dependent solubility, 94.3 mg/mL to 2.37 mg/mL at pH values from 1 to 9.

Due to its mood stabilizing effects, recently, quetiapine has gained attention as a treatment option in patients with bipolar affective disorder and major depression. Thus, the objective of the present paper was to evaluate, by means of response surface methodology, the influence of oil, surfactant, and cosurfactant on the particle size, zeta potential, and on drug release from SNEDDS. As a part of optimization process, the main effects, interaction effects, and quadratic effects of the formulation ingredients were evaluated for their effect on the particle size of quetiapine fumarate SNEDDS. Particle size is particularly important since release rates are greatly influenced by particle size. Zeta potential also confers stability of an emulsion.

MATERIALS AND METHODS

Materials

Quetiapine Fumarate was a received from Glenmark Pharmaceutical Pvt. Ltd., as a gift sample. Labrafac Lipophile WL 1349 and Capryol 90 were received as a gift sample from Gattefosse. All other chemicals/reagents were used of analytical grade and double-distilled water used throughout the experiments.

Preparation of the quetiapine fumarate self-nano-emulsifying formulation

A series of SNEDDS formulations was prepared using Tween 80/Capryol 90 as the surfactant/cosurfactant (S/CoS) combination and Labrafac Lipophile WL as the oil was given in [Tables 1 and 2]. In all the formulations, the level of the quetiapine fumarate was kept constant (25 mg). Briefly, accurately weighed the quetiapine fumarate was placed in a glass vial, and oil, surfactant, and co-surfactant were added. Then, the components were mixed by gentle stirring and vortex mixing and were heated at 40°C on a magnetic stirrer, and afterward, the mixture was sonicated on probe sonicator until the quetiapine fumarate was perfectly dissolved. The mixture was stored at room temperature until further study.

Determination of particle size

Particle size distribution following self-micro emulsification is a critical factor to evaluate a self-microemulsion system. The droplet size of the optimized formulation was measured using Zetasizer (Malvern Instrument, UK). The instrument generally works by photon correlation spectroscopy that measures the light scattering The particle size distribution and polydispersity index of various formulations are summarized in Table 3. An increase in the concentration of the oil phase (Labrafac Lipophile WL 1349) resulted in a proportional increase in particle size because of the simultaneous decrease in the S/CoS proportion. Increasing the S/CoS ratio led to decrease in mean droplet size. It is well known that the addition of surfactants to the microemulsion system causes the interfacial film to stabilize and condense, while the addition of co-surfactant causes the film to expand; thus, the relative proportion of surfactant to co-surfactant has varied effects on the particle size.

Polydispersability index below 0.3 indicates good uniformity in the globule size distribution after dilution with water.

Table 1: Coded formulation

Coded level	Low level (−1)	High level (+1)
X_1 (oil)	0.10	0.20
X_2 (surfactant)	0.52	0.60
X_3 (cosurfactant)	0.28	0.30

Determination zeta potential

The zeta potential indicates the degree of repulsion between adjacent, similarly charged particles in dispersion. For molecules and particles that are small enough, a high zeta potential will confer stability. The zeta potential of the optimized SNEDDS is given in Table 3.

Table 2: Formulation of SMEDDS of quetiapine fumarate

Formulation code	Surfactant (ml)	Cosurfactant (ml)	Oil (ml)
F1	0.52	0.28	0.10
F2	0.52	0.28	0.15
F3	0.52	0.28	0.20
F4	0.56	0.28	0.10
F5	0.56	0.28	0.15
F6	0.56	0.28	0.20
F7	0.60	0.28	0.10
F8	0.60	0.28	0.15
F9	0.60	0.28	0.20
F10	0.52	0.29	0.10
F11	0.52	0.29	0.15
F12	0.52	0.29	0.20
F13	0.56	0.29	0.10
F14	0.56	0.29	0.15
F15	0.56	0.29	0.20
F16	0.60	0.29	0.10
F17	0.60	0.29	0.15
F18	0.60	0.29	0.20
F19	0.52	0.30	0.10
F20	0.52	0.30	0.15
F21	0.52	0.30	0.20
F22	0.56	0.30	0.10
F23	0.56	0.30	0.15
F24	0.56	0.30	0.20
F25	0.60	0.30	0.10
F26	0.60	0.30	0.15
F27	0.60	0.29	0.20

SMEDDS: Self-microemulsifying drug delivery system

Table 3: Evaluation of SMEDDS

Formulation	Particle size (nm)	Zeta potential (mv)	Drug release (%)	Polydispersibility index
F1	96.74	−11.36	93.003	0.0933
F2	88.36	−11.69	98.251	0.0700
F3	79.49	−4.59	92.787	0.0510
F4	97.74	−15.54	99.354	0.0920
F5	99.48	−5.68	99.165	0.1830
F6	81.26	−11.36	99.921	0.0440
F7	97.49	−8.98	98.348	0.0440
F8	86.74	−15.66	96.404	0.1040
F9	89.74	−15.54	99.077	0.0780
F10	79.46	−16.21	96.429	0.1260
F11	78.88	−8.98	92.501	0.0680
F12	79.56	−10.36	96.262	0.1740
F13	99.74	−16.98	92.997	0.0900
F14	98.45	−6.39	92.811	0.1360
F15	99.74	−8.36	92.753	0.0900
F16	89.46	−14.56	90.984	0.2830
F17	28.36	−15.36	94.922	0.1960
F18	35.36	−10.56	90.626	0.1850
F19	25.37	−14.56	98.155	0.1013
F20	95.74	−18.84	92.456	0.0940
F21	90.74	−16.69	91.001	0.0770
F22	40.12	−18.65	94.026	0.0610
F23	26.37	−14.69	99.077	0.0970
F24	54	−17.95	98.035	0.1640
F25	39.37	−6.98	90.866	0.0390
F26	96.74	−7.87	90.212	0.0930
F27	50.6	−11.25	88.9	0.0510

SMEDDS: Self-microemulsifying drug delivery system

In vitro dissolution study

All quetiapine fumarate SNEDDS formulation released study was carried out using dissolution apparatus paddle type using cellophane membrane with dissolution medium as 0.1 N hydrochloric acid, and all formulations approximately show release above 90% within 60 min as given in Table 3. It could be suggested that the SNEDDS formulation resulted in spontaneous formation of a microemulsion with a small particle size, which permitted a faster rate of drug release into the aqueous phase. Thus, this greater availability of dissolved quetiapine fumarate from the self-microemulsifying drug delivery system formulation could lead to higher absorption and higher oral bioavailability. It was also showed that increase in surfactant concentration and decrease in oil concentration in formulation increase the drug release.

Experimental design

A 3^3 randomized full factorial design was applied in the present study. In the design, 3 factors were evaluated, each at 3 levels, and experimental trials were performed at all 27 possible combinations. These are usually referred to as low, intermediate, and high levels. These levels are numerically expressed as 0, 1, and 2 or −1, 0, and +1. A study, in which there are three factors with 3 levels, is called a 3^3 factorial design. The concentration of surfactant, concentration of cosurfactant, and concentration of oil were used as independent variables. The particle size, zeta potential, and drug release were used as dependent variables. The experimental design consists of a set of points lying at the midpoint of each edge and replicated center point of the multidimensional cube. The independent and dependent variables are listed in Table 1. The polynomial equation generated by this experimental design (using design expert software version7.0) is as follows:

$$Yi = b0 + b1X1 + b2X2 + b3X3 + b12X1X2 + b13X1X3 + b23X2X3 + b11X12 + b22X22 + b33\ X32$$

Where Yi is the dependent variable, b0 is the intercept, b1 to b33 are the regression coefficients, and X1, X2, and X3 are the independent variable that was selected from the preliminary experiments. The model generated contained quadratic terms which explained the non-linear nature of responses and multiple factor terms explaining effects between factors. The formulation was optimized with the help of response surface diagram.

RESULTS AND DISCUSSION

Construction of phase diagram

Pseudo-ternary phase diagrams of oil, S/CoS, and water were developed using the water titration method. The mixtures of oil and S/CoS at certain weight ratios were diluted with water in a drop-wise manner. For each phase diagram at a specific ratio of S/CoS (i.e.,1:1, 2:1, 3:1, 1:2, and 1:3 wt/wt), a transparent and homogenous mixture of oil and S/CoS was formed by vortexing for 5 min. Then, each mixture was titrated with water and visually observed for phase clarity and flowability. The concentration of water at which turbidity-to-transparency and transparency-to-turbidity transitions occurred was derived from the weight measurements. These values were then used to determine the boundaries of the microemulsion domain corresponding to the chosen value of oils, as well as the S/CoS mixing ratio. To determine the effect of drug addiction on the microemulsion boundary, phase diagrams were also constructed in the presence of drug using drug-enriched oil as the hydrophobic component. Phase diagrams were then constructed using Chemix Software as shown in Figures 1-5. Ratio 2:1 further selected as it shows maximum area and no separation of phases.

Optimization

Effect of excipients on drug release and model fitting

According to applied 3^3 experimental designs, 27 experiments were performed to optimize the formulation method of SNEDDS to get maximum drug release in terms of response. The obtained results were entered in design expert software 7.0.0 as shown in [Table 4].

As shown in [Table 4] the model *F* value of 2.58 implies that the model is statistically significant. There is only a 4.43% chance that a "model *F* value" this large could occur due to noise. Values of "$P > F$" <0.0500 indicate that model terms are statistically significant. In this case C, BC is significant model terms.

Final equation in coded factors

$$\text{Drug Release (Y)} = +95.28 - 0.18*A - 0.58*B - 1.94*C + 0.50*A*B - 0.39*A*C - 1.78*B*C - 0.53*A^2 - 2.34*B^2 + 2.06*C^2$$

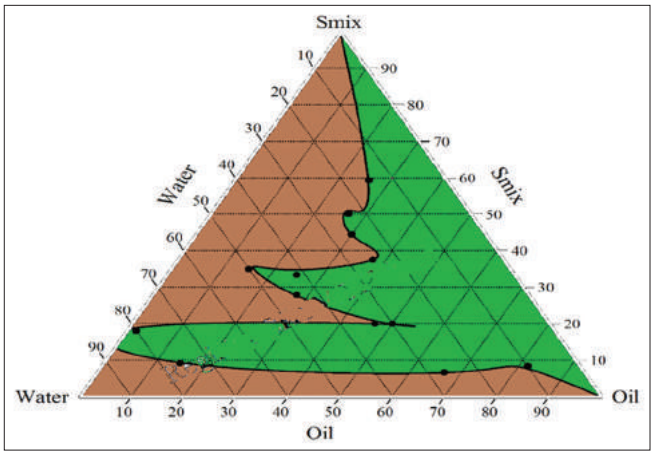

Figure 1: Pseudo-ternary phase diagrams with the following excipients: Oil-Labrafac Lipophile, surfactant-Tween 80, and cosurfactant-Capryol 90. Smix ratio of 1:1. Smix indicates surfactant/cosurfactant

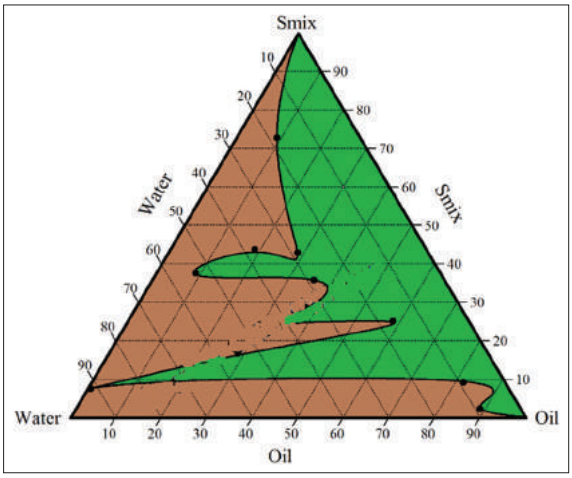

Figure 2: Pseudo-ternary phase diagrams with the following excipients: Oil-Labrafac Lipophile, surfactant-Tween 80, and cosurfactant-Capryol 90. Smix ratio of 2:1. Smix indicates surfactant/cosurfactant

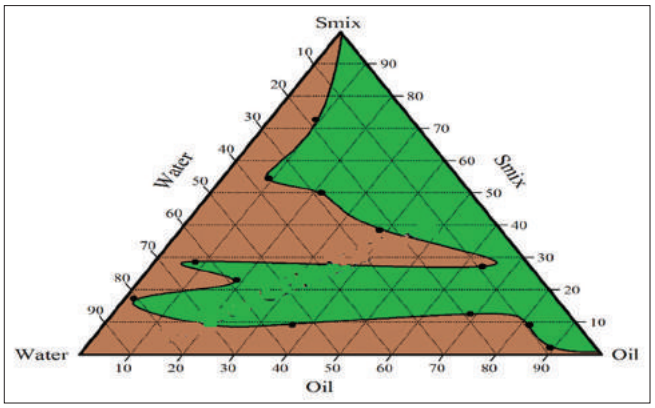

Figure 3: Pseudo-ternary phase diagrams with the following excipients: Oil-Labrafac Lipophile, surfactant-Tween 80, and cosurfactant-Capryol 90. Smix ratio of 3:1. Smix indicates surfactant/cosurfactant.

Table 4: Analysis of variance and model equation (% drug release)

Source	Sum of squares	df	Mean square	*F* value	*P* value Prob>*F*
Model	177.67	9	19.74	2.58	0.0443
A-Labrafac Lipophile	0.61	1	0.61	0.079	0.7815
B-Tween 80	6.09	1	6.09	0.80	0.3850
C-Capryol 90	68.06	1	68.06	8.89	0.0084
AB	2.98	1	2.98	0.39	0.5412
AC	1.84	1	1.84	0.24	0.6303
BC	38.11	1	38.11	4.98	0.0394
A^2	1.67	1	1.67	0.22	0.6465
B^2	32.39	1	32.39	4.30	0.0537
C^2	25.42	1	25.42	3.32	0.0861
Residual	130.18	17	7.66		
Cor total	307.85	26			

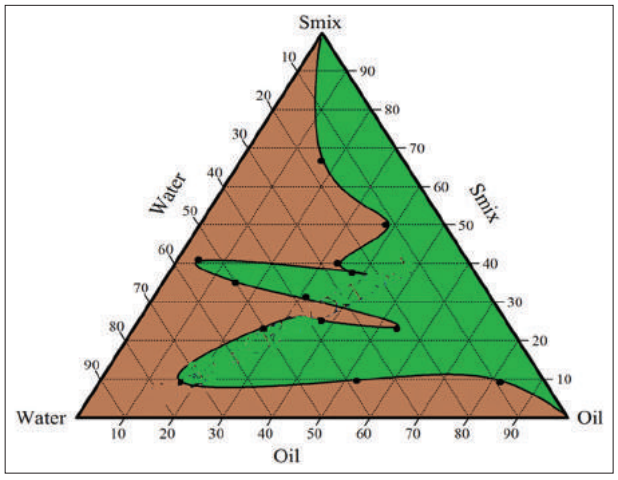

Figure 4: Pseudo-ternary phase diagrams with the following excipients: Oil-Labrafac Lipophile, surfactant-Tween 80, and cosurfactant-Capryol 90. Smix ratio of 1:2. Smix indicates surfactant/cosurfactant

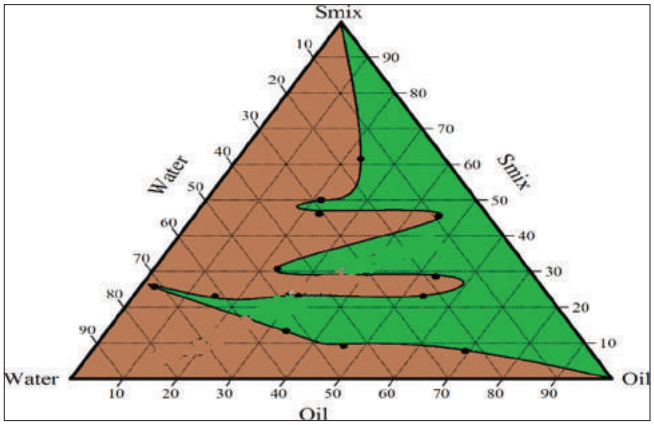

Figure 5: Pseudo-ternary phase diagrams with the following excipients: Oil-Labrafac Lipophile, surfactant-Tween 80, and cosurfactant-Capryol 90. Smix ratio of 1:3. Smix indicates surfactant/cosurfactant

Final equation in actual factors

Drug release(Y) = +690.95473 +147.2494* Labrafac Lipophile +2879.17778 * Tween 80 −9519.6361 * Capryol 90+249.08333* Labrafac Lipophile * Tween 80 −783.16667 * Labrafac Lipophile * Capryol 90 −4455.4166 * Tween 80 * Capryol 90 −210.97778* Labrafac Lipophile^2 −1463.40278 * Tween 80^2 +20582.22222* Capryol 90^2

The above final equation represents the independent variable quantitative effect and their interaction on the response. The values of the coefficients A, B, and C related to the effect of these variables on the response Y. Coefficient with more than one-factor term and those with higher order terms represent interaction term. A positive sign indicates a synergistic effect, while a negative sign indicates an antagonist effect.

Counter plot and three-dimensional (3D) graphical presentations 3D surface for drug release

Figures 6 and 7 show the counterplot and 3D surface, respectively, for Labrafac Lipophile, Tween 80, and Capryol 90. It appears as A and B concentration increases, % drug release was found to be increased at some level, and then, there is a decrease in % drug release as concentration of A and B increases at fixed level of C.

Effect of excipient on particle size

Table 5 indicates the model F value of 2.83 implies that the model is statistically significant. There is only a 3.70 % chance that a "Model *F* value" this large could occur due to noise. Values of "Prob > *F*" <0.0500 indicate that model terms are statistically significant. In this case B, C is significant model terms [Table 5].

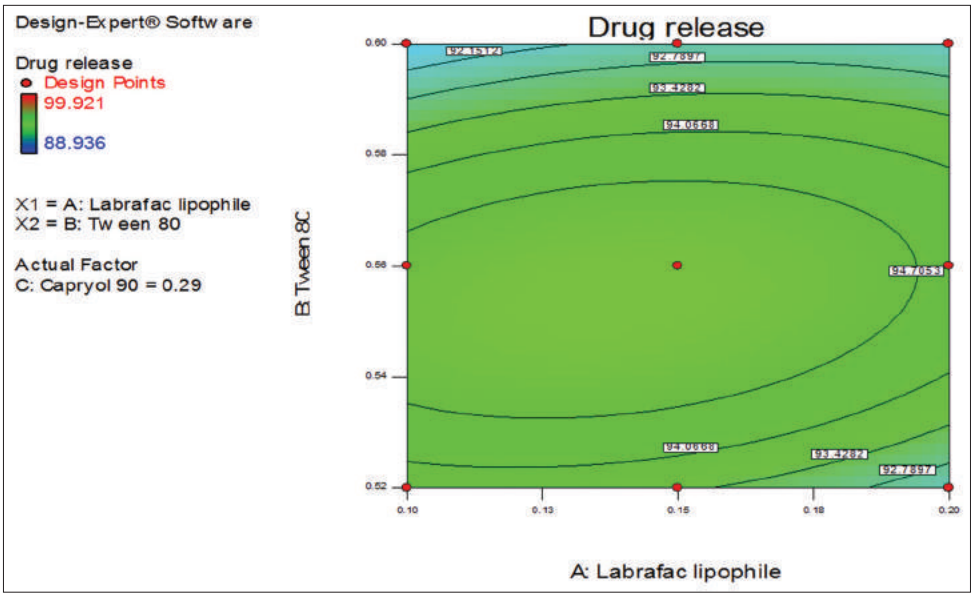

Figure: 6 Contour plot the effect of Labrafac Lipophile, Tween 80 on % drug release

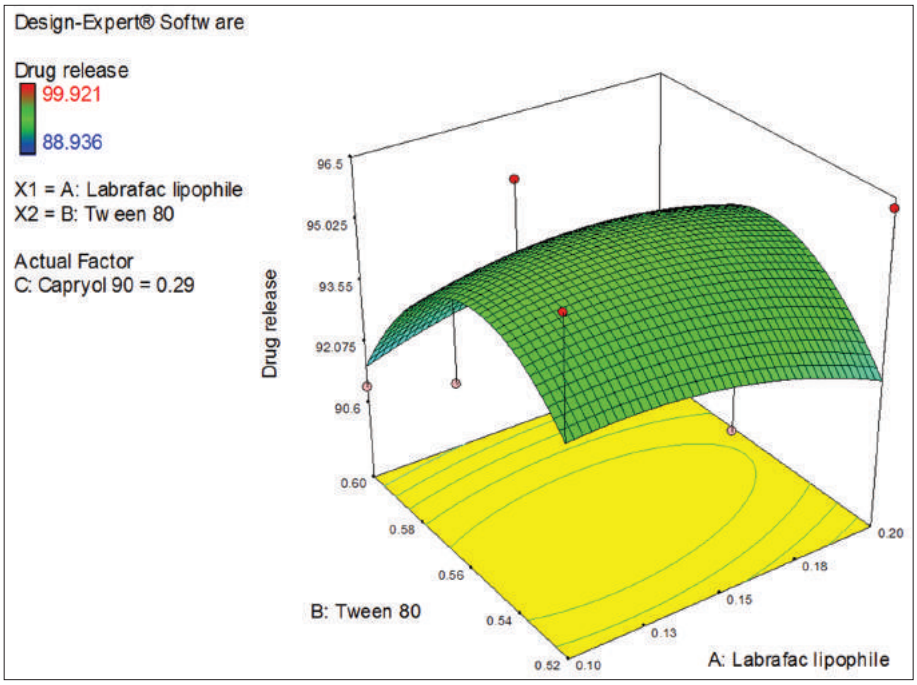

Figure 7: Three-dimensional surface plot of percent drug release

Final equation in terms of coded factors

Particle size (Y2)=+73.60 −2.38 * A-6.71* B-18.6 * C-9.92 * A * B+7.84* A * C −4.5* B * C

Final equation in terms of actual factors

Particle size (Y2)= −871.86907−1814.42222* Labrafac Lipophile + 3885.00000 * Tween 80 + 2171.5000* Capryol 90 −4961.66667 * Labrafac Lipophile * Tween 80 + 15673.33333 * Labrafac Lipophile * Capryol 90 −11408.3333 * Tween 80 * Capryol 90

Counter plot and 3D graphical presentations 3D surface for particle size

Figures 8 and 9 demonstrate the counterplot and 3D of Labrafac Lipophile, Tween 80 at fixed level of Capryol 90 individually. It appears as Labrafac Lipophile and Tween 80 increment, there is a decrease in particle size.

Effect of excipients on zeta potential

The model *F* value of 2.64 implies that the model is statistically significant. There is only a 4.76% chance that a

"model *F* value" this large could occur due to noise. Values of "Prob > *F*" <0.0500 indicate that model BC is significant model terms [Table 6].

Final equation in terms of coded factors

Zeta potential (Y3)= −12.43 +0.95 * A +0.36 * B −1.50 * C −1.4 * A * B −0.84 * A *C+3.04* B * C

Final equation in terms of actual factors

Zeta potential (Y3)= +1125.42583 +910.88333* Labrafac Lipophile −2089.71528 * Tween 80 −4160.02778* Capryol 90 −721.66667 * Labrafac Lipophile * Tween 80 −1681.66667 *Labrafac Lipophile * Capryol 90 +7610.41667* Tween 80 * Capryol 90

Counter plot and 3D graphical presentations 3D surface for zeta potential

Figures 10 and 11 illustrate the counterplot and 3D of Labrafac Lipophile, Tween 80 at fixed level of Capryol 90 individually. It was found that as Labrafac Lipophile and Tween 80 concentration increases, there was an increase in zeta potential. It was concluded from the graph that the factor A has a significant effect on the zeta potential.

Optimization of formulation

For the model validation, the two formulations were prepared. The values of response predicted from the obtained model are shown in Table 7, along with result obtained by experimentation. The close resemblance between observed and predicted response values assessed the robustness of

Table 5: Analysis of variance and model equation (particle size)

Source	Sum of squares	df	Mean square	*F* value	*P* value Prob>*F*
Model	9349.13	6	1558.19	2.83	2.83
A-Labrafac Lipophile	102.34	1	102.34	0.19	0.67
B-Tween 80	809.63	1	809.63	1.47	0.024 significant
C-Capryol 90	6268.64	1	6268.64	11.37	0 significant
AB	1181.67	1	1181.67	2.14	0.16
AC	736.96	1	736.96	1.34	0.26
BC	249.89	1	249.89	0.45	0.51
Residual	11024.64	20	551.23		
Cor total	20373.77	26			

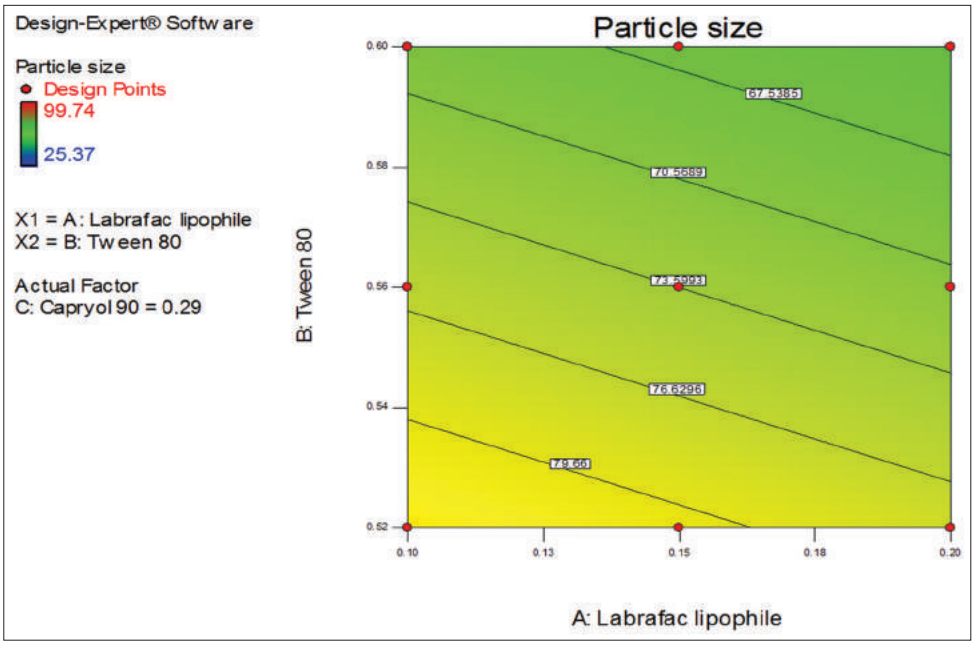

Figure 8: Contour plot the effect of Labrafac Lipophile, Tween 80, and Capryol 90 on particle size

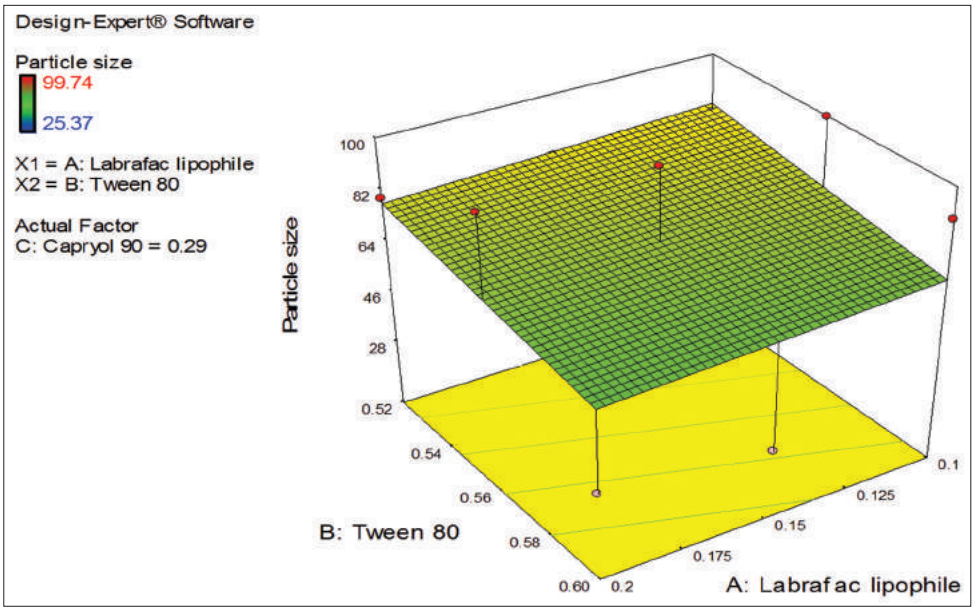

Figure 9: Three-dimensional surface plot of particle size of quetiapine with respect to Labrafac Lipophile, Tween 80, and Capryol 90

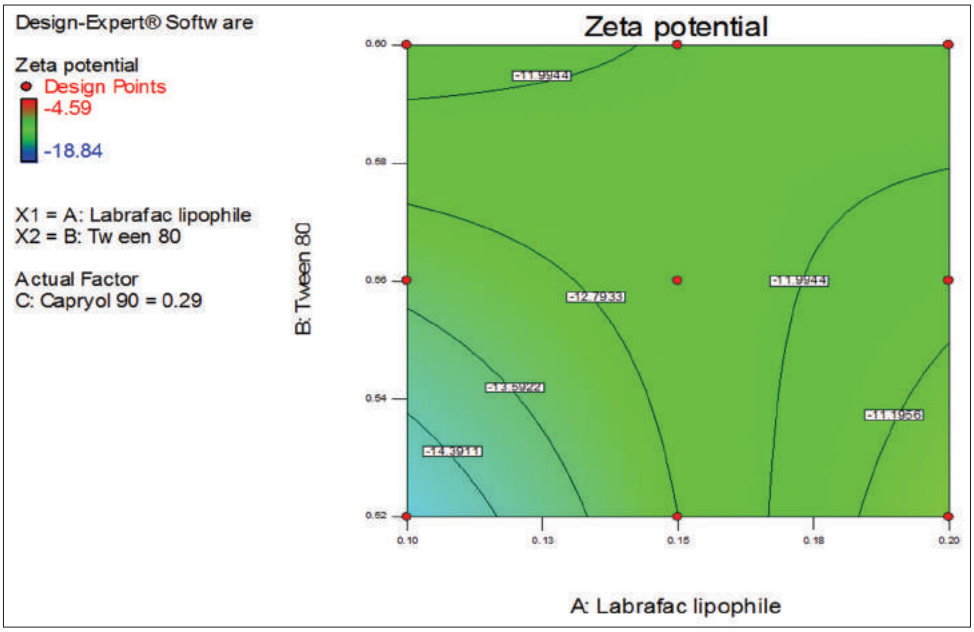

Figure 10: Contour plot the effect of Labrafac Lipophile, Tween 80, and Capryol 90 on zeta potential

the predictions. These values indicate the validity of the generated model.

Residual plots show for particle size, zeta potential, and percent drug release indicates points nearly closed to straight lines indicating good model as shown in [Figures 12-14] respectively. The model term for the particle size, drug release, and zeta potential was found with a value of r^2 0.4589, 0.5771, and 0.4416. This may obtain because when we run design expert using levels X3 and X4, having the independent factor levels closer together generate a smaller signal-to-noise ratio and cause r^2 smaller.

CONCLUSION

Optimization of the SNEDDS formulation of quetiapine fumarate was performed using 3 factor, 3 level design. The amount of added A (Labrafil 2609 WL), B (Labrasol), and C (Cremophor EL) showed a significant effect on the particle size, drug release, and zeta potential.

The quantitative effect of these factors at different levels was predicted using polynomial equation. Response methodology was then used to predict the levels of the factors A, B, and C required to obtain an optimum formulation. A new formulation

Table: 6 Analysis of variance and model equation (zeta potential)

Source	Sum of squares	df	Mean square	*F* value	*P* value Prob>*F*
Model	204.15	6	34.02	2.64	0.0476
A-Labrafac Lipophile	16.36	1	16.36	1.27	0.2736
B-Tween 80	2.36	1	2.36	0.18	0.6734
C-Capryol 90	40.74	1	40.74	3.16	0.0909
AB	25.00	1	25.00	1.94	0.1793
AC	8.48	1	8.48	0.66	0.4271
BC	111.20	1	111.20	8.61	0.0082
Residual	258.17	20	12.91		
Cor total	462.32	26			

Table 7: Formulation optimization

Variables	Quantity	Predicted particle size	Observed particle size	Predicted drug release	Observed drug release	Predicted zeta potential	Observed zeta potential
Tween 80	0.57 ml						
Labrafac Lipophile	0.19 ml	54.425	50.6	93.679	88.9	−13.035	−11.25
Capryol 90	0.30 ml						

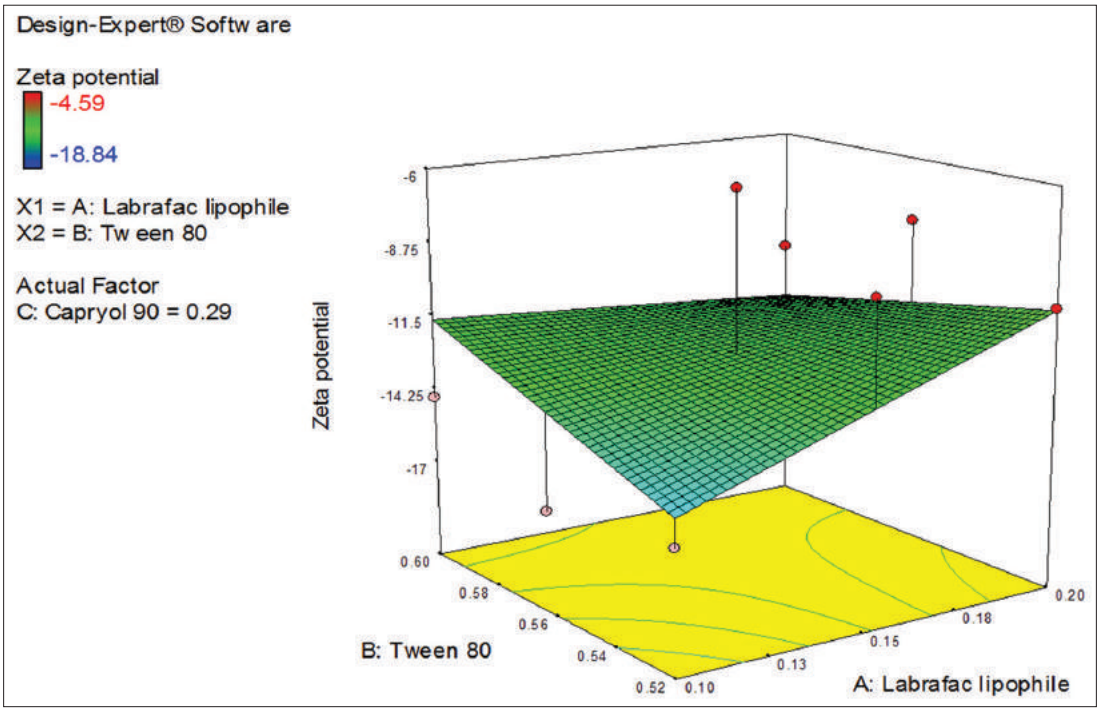

Figure 11: Three-dimensional surface plot of zeta potential of quetiapine with respect to Labrafac Lipophile, Tween 80, and Capryol 90

was prepared according to these levels. Signal-to-noise ratio was studied. Observed response was in close agreement with the predicted values of the optimized formulation, thereby demonstrating the feasibility of the optimization procedure in developing self-micro emulsifying delivery of quetiapine fumarate.

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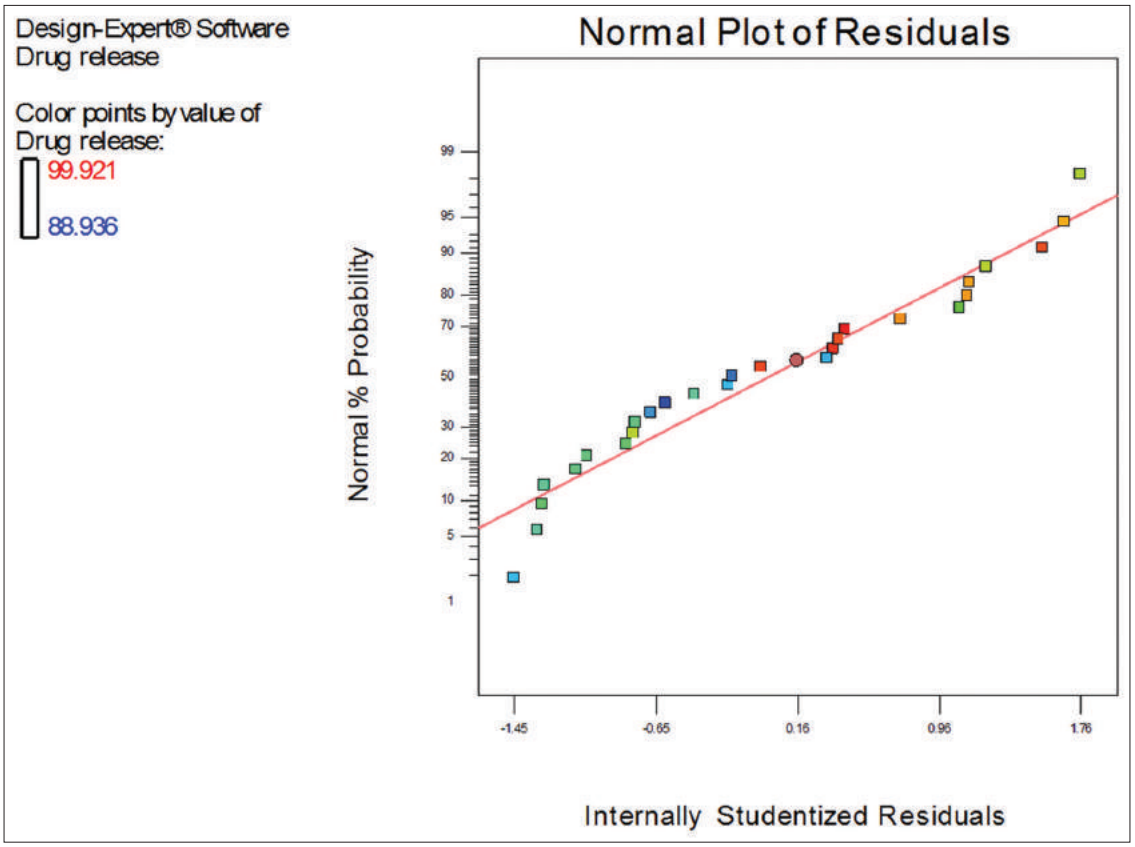

Figure 12: Residual plot for drug release

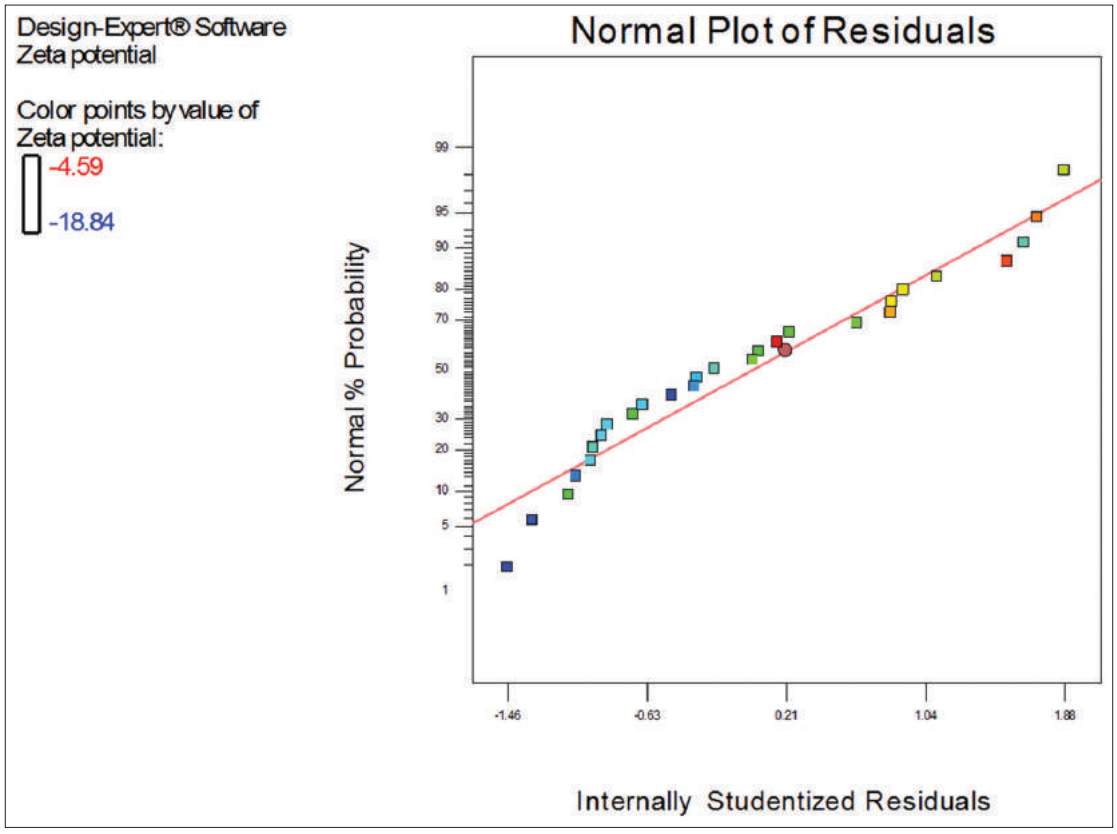

Figure 13: Residual plot for particle size

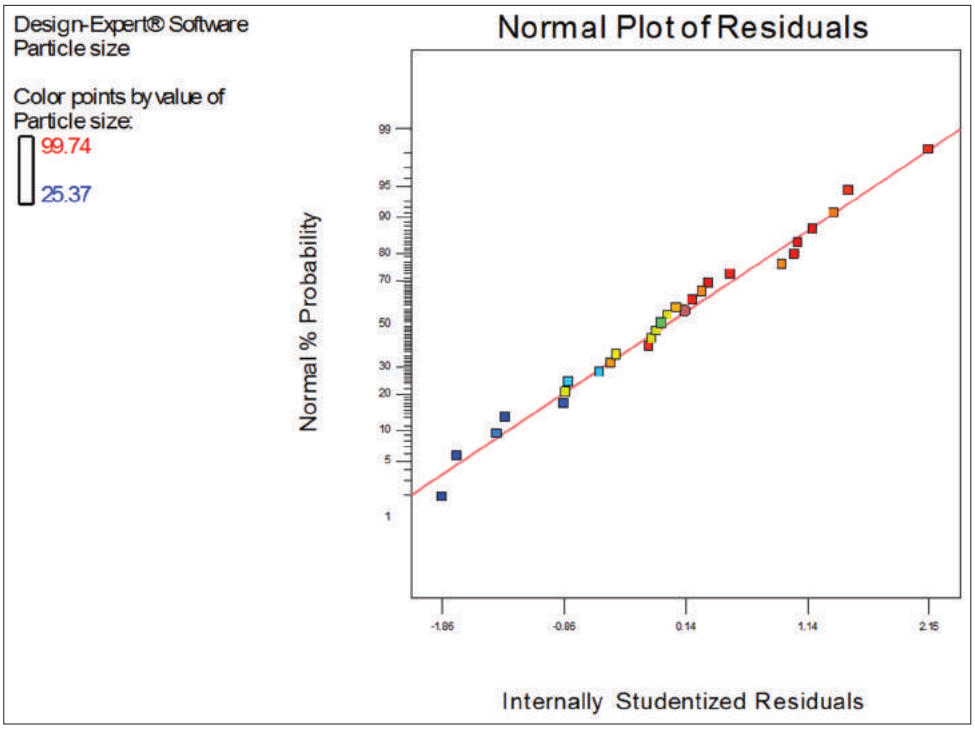

Figure 14: Residual plot for zeta potential

REFERENCES

1. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutical drug classification: The correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res 1995;12:413-20.
2. Shaji J, Lodha S. Response surface methodology for the optimization of celecoxib self-microemulsifying drug delivery system. Indian J Pharm Sci 2008;70:585-90.
3. Villar AM, Naveros BC, Campmany AC, Trenchs MA, Aróztegui M, Rocabert B, *et al*. Design and optimization of self-nanoemulsifying drug delivery systems (SNEDDS) for enhanced dissolution of gemfibrozil. Int J Pharm 2012;431:161-75.
4. Porter CJ, Pouton CW, Cuine JF, Charman WN. Enhancing intestinal drug solubilisation using lipid-based delivery systems. Adv Drug Deliv Rev 2008;60:673-91.
5. Talele S, Gudsoorkar VR. Novel approaches for solidification of SMEDDS. Int J Pharm Biosci 2016;15:90-101.
6. Singh B, Bhatowa R, Tripathi CB, Kapil R. Developing micro-nanoparticulate drug delivery systems using design of experiment. Int J Pharm Invest 2011;1:75-87.
7. Nazzal S, Smalyukh II, Lavrentovich OD, Khan MA. Preparation and *in vitro* characterization of a eutectic based semisolid self-nanoemulsified drug delivery system (SNEDDS) of ubiquinone: Mechanism and progress of emulsion formation. Int J Pharm 2002;235:247-65.
8. Holm R, Jensen IH, Sonnergaard J. Optimization of self-microemulsifying drug delivery systems using a D-optimal design and the desirability function. Drug Dev Ind Pharm 2006;32:1025-32.
9. Cutler AJ, Goldstein JM, Tumas JA. Dosing and switching strategies for quetiapine fumarate. Clin Ther 2002;24:209-22.
10. Ihor WR, Lisa AA. Overview of the efficacy of seroquel (quetiapine). Schizophr Res 1997;24:199.
11. King DJ, Link CG. Seroquel (ICI 204636): An atypical antipsychotic results from Phase III. E Neuro 1996;6:202.

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