

Development and Characterization of Self-nano-emulsifying Drug-delivery System for Oral Delivery of Verapamil

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Abstract

Introduction: The present study deals with the development and characterization of self-nano-emulsifying drug-delivery system (SNEDDS) to improve the oral bioavailability of water-insoluble biopharmaceutical classification system Class II drug verapamil. The objectives of the study are to develop SNEDDS of verapamil and to characterize for particle size, self-nano-emulsification, and dissolution enhancement. Solubility of verapamil was determined in various oils, surfactants, and cosurfactants. **Materials and Methods:** Captex 355 was selected as an oil phase, acrysol K140 as surfactant, and PEG400 as cosurfactant due to their higher solubilization effect. **Results:** Various formulations were prepared by simple mixing followed by vortexing. From studies, the optimized SNEDDS formulation was composed of verapamil (9.13% w/w), captex 355 (23.41% w/w), acrysol K140 (51.62% w/w), and PEG 400 (11.58% w/w). The selected SNEDDS could be self-emulsified without precipitation on simple mixing. The mean particle size of the SNEDDS was 148.7 nm and percent drug content was 99.66. The *in vitro* dissolution of verapamil from SNEDDS was found to be significantly higher (95.4 ± 2.07) in comparison to the marketed tablet (64.8 ± 1.36) and pure drug (52.5 ± 1.65) in 0.1 N HCl as dissolution medium. **Conclusion:** The results indicate that SNEDDS of verapamil, due to its nanosized, has potential to enhance the absorption of drug due to its higher dissolution.

Key words: Dissolution rate, Droplet size, Self-nano-emulsification, Verapamil

INTRODUCTION

The Class II to Class IV drugs of biopharmaceutical classification system suffering with poor water solubility lead to lower intestinal absorption and lower bioavailability. Solubilizing poor water-soluble drugs are a major challenge in pharmaceutical research.^[1] Lipid-based drug formulations increase the relative solubility of drugs in gastrointestinal (GI) track by enhancing absorption. Self-nano-emulsifying drug-delivery systems (SNEDDS) lipid-based formulations are most promising technology in drug delivery. SNEDDS is defined as pre-concentrate containing a mixture of drug, surfactants, oil, and cosurfactant. The smaller size of SNEDDS improves drug dissolution by increasing area for drug release, absorption, and by promoting lymphatic transport of the drug. SNEDDS formulation is used for increasing the solubility, oral bioavailability, and permeability of drug. It also protects the drug from hostile environment in GI track and is used for selective GI targeting

drug delivery.^[2] They have particle size ranging from nanometers to few microns. Based on particle size, they are, further, classified into SMEDDS and SNEDDS. SMEDDS forms microemulsions consisting of oil droplet size ranging between 100 and 200 nm. SNEDDS contains the droplets whose size is <100 nm.^[3] Verapamil regularly reduces the total peripheral resistance (after load) against the heart, which works both at rest and at a given level of exercise by dilating peripheral arterioles. This unloading of the heart reduces myocardial energy consumption and oxygen requirements and probably accounts for the effectiveness of verapamil in chronic stable effort angina. The mechanism of the anti-anginal effect of verapamil is believed to be related to its specific

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Received: 23-09-2022

Revised: 07-11-2022

Accepted: 14-11-2022

cellular action of selectively inhibiting transmembrane influx of calcium in cardiac muscle, coronary, and systemic arteries and in cells of the intracardiac conduction system. Verapamil blocks the transmembrane influx of calcium through the slow channel (calcium ion antagonism) without affecting to any significant degree the transmembrane influx of sodium through the fast channel. This results in a reduction of free calcium ions available within cells of the above tissues. Verapamil exerts anti-hypertensive effects by inducing peripheral vasodilatation and reducing peripheral vascular resistance usually without reflex tachycardia. These effects are mediated by inhibition of calcium ion influx into smooth muscle cells of the arteriolar wall.^[4] The objective of present research is to design and characterize the liquid SNEDDS of verapamil. The ability of SNEDDS to improve dissolution rate is evaluated. The formulated SNEDDS was characterized for emulsification time, percentage transmittance, particle size, drug release, and thermodynamic stability.

MATERIALS AND METHODS

Materials

Verapamil is gifted by Aurobindo pharma limited, Hyderabad. Captex 355 and Acrysol K140 and PEG400 were procured from Gattefosse, Mumbai.

Preparation of verapamil-loaded SNEDDS

The verapamil-loaded SNEDDS was prepared by mixing oil phase (Captex 355), surfactant (Acrysol K140), and cosurfactant (PEG 400) and warming it at 40°C; then, verapamil was added to the mixture and vortexed to facilitate the uniform dispersion of verapamil. The mixture was then allowed to equilibrate at room temperature. Seventeen such experiments were carried out according to the experimental design with varying concentration of oil, surfactant, and cosurfactant, with the final verapamil loading equivalent to 2 mg/g. Verapamil (80 mg) added to oil into the glass vial and heated in hot water bath at 40°C until drug solubilized. Then to this, oily mixture was added surfactant and cosurfactant and sonicated for 60 min. The prepared verapamil-loaded SNEDDS was filled into size 0 gelatin capsule shells.^[5]

Preparation of verapamil standard stock solution

10 mg of working standard verapamil were transferred into a 10 ml volumetric flask and were added 1 ml of phosphate buffer pH 1.2 until the mark to obtain a solution of 1000 µg/ml. The solution diluted with phosphate buffer to get a solution concentration of 100 µg/ml. From this solution, a series of aliquots was prepared for further method development.^[6]

Characterization of SNEDDS

Developed verapamil SNEDDSs were physicochemically evaluated in terms of droplet diameter, polydispersity index (PI), zeta potential (ZP), entrapment efficiency, drug content, and cumulative% drug release.

Droplet size and polydispersity index

Droplet size and polydispersity index of 17 different liquid SNEDDS formulations (2 mg), each containing 5% verapamil, were prepared. Then, 2 mg of each formulation was diluted in 100 mL deionized water in a beaker maintained at 37°C and gently stirred using a magnetic stirrer. All samples were subjected to a brief period of sonication to minimize any aggregation if present using a bath sonicator (Frontline FS-4, Mumbai, India). The droplet size of the resulting emulsion was immediately determined by a Zetasizer Nano ZS90 dynamic light scattering particle size analyzer (Malvern Instruments, Malvern, Worcestershire, UK) at a wavelength of 278 nm,

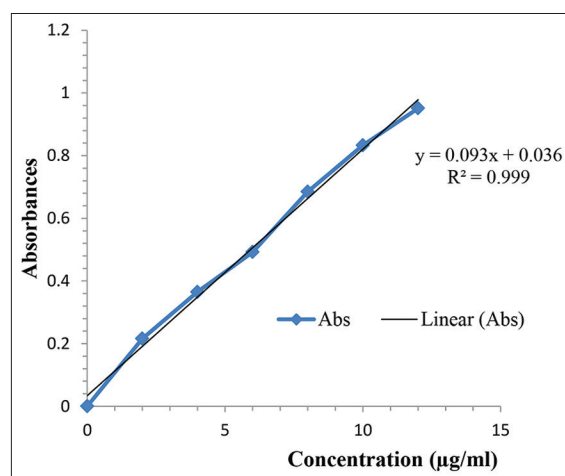


Figure 1: Standard calibration graph of Ramipril in pH 6.8 phosphate buffer

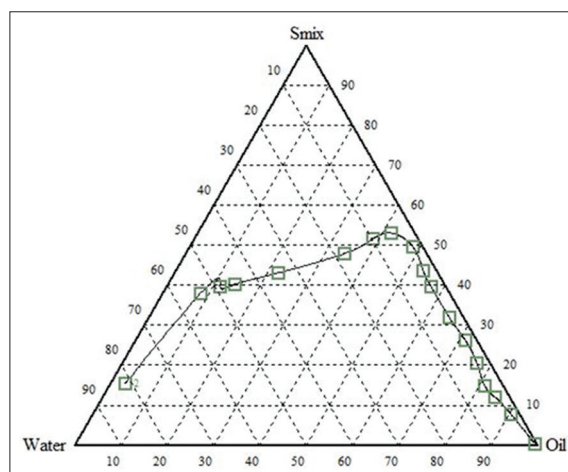


Figure 2: Pseudo tertiary graph of Smix ratio 1:1

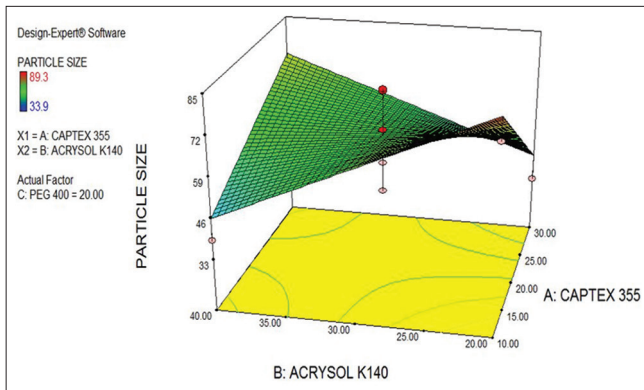


Figure 3: Response 3D surface plot showing the influence of amount of captex 355 and amount of acrysol K140 on droplet size fixed level of C

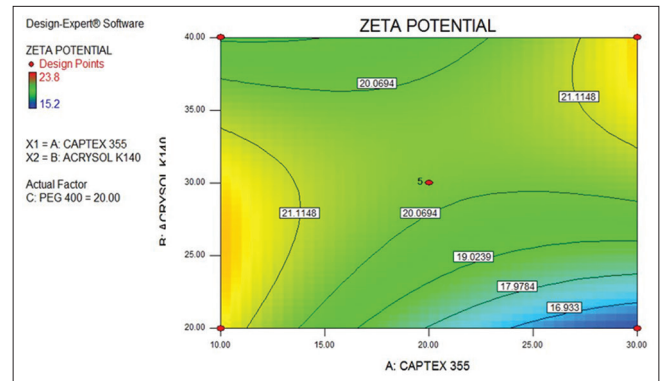


Figure 6: Contour plots showing the influence of amount of captex 355 and amount of acrysol K140 on ZP level of C

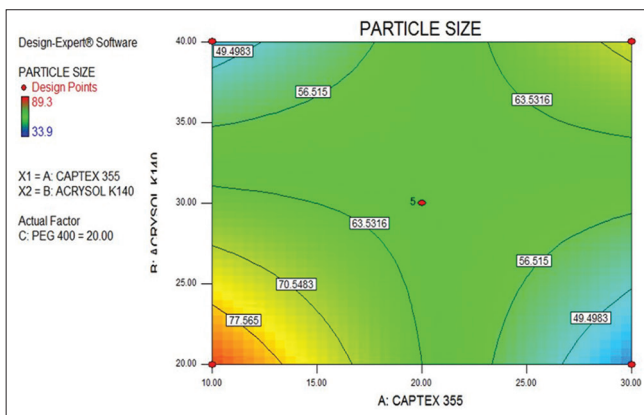


Figure 4: Contour plot showing the influence of amount of captex 355 and amount of acrysol K140 on droplet size fixed level of C

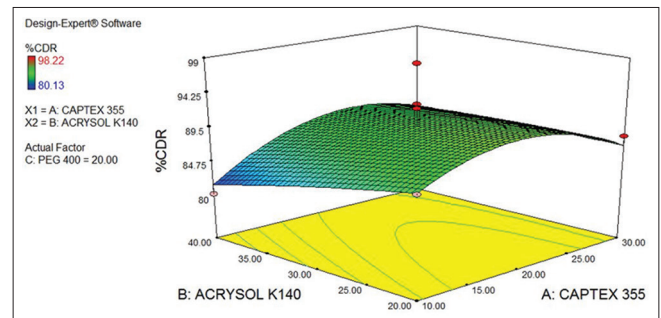


Figure 7: Response 3D surface plot showing the influence of amount of captex 355 and amount of acrysol K140 on cumulative% drug released level of C

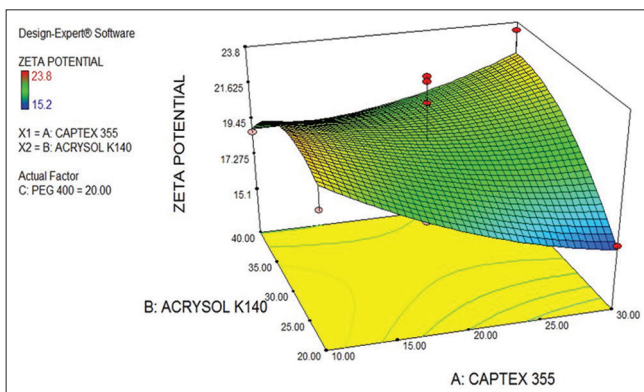


Figure 5: Response 3D surface plot showing the influence of amount of Captex 355 and amount of Acrysol K140 on Zeta Potential (ZP) level of C

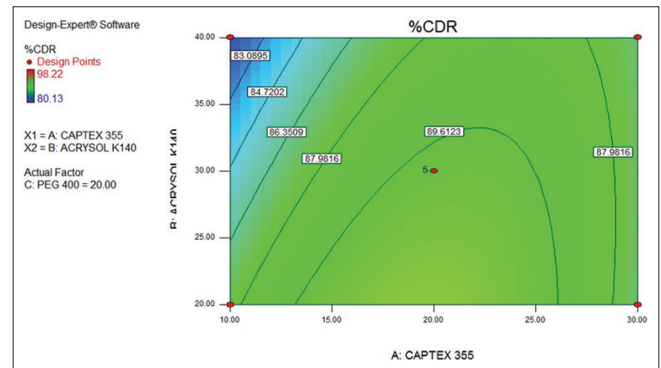


Figure 8: Contour plot showing the influence of amount of captex 355 and amount of acrysol K140 on cumulative% drug released of C

a scattering angle of 90° and at 25°C. All of the studies were carried out in triplicate and the values of z-average diameters were used. The polydispersity index (PDI) and z-average diameter, also referred to as the harmonic intensity-weighted average hydrodynamic diameter of the emulsion, were derived from cumulated analysis by Auto measure software.^[7]

ZP

The ZP (z) values were evaluated for all experimental design batches of verapamil-loaded SNEDDS by determining the particle electrophoretic mobility using particle size analyzer. The method employed for the sample preparation was similar to that of globule size measurement. The analysis was performed in purified water (pH 5.5–6.0) adjusted to a standardized conductivity of 50 mS/cm with sodium chloride solution (0.9% w/v) to avoid changes in z values due to day-to-day variations occurring in the conductivity of water.

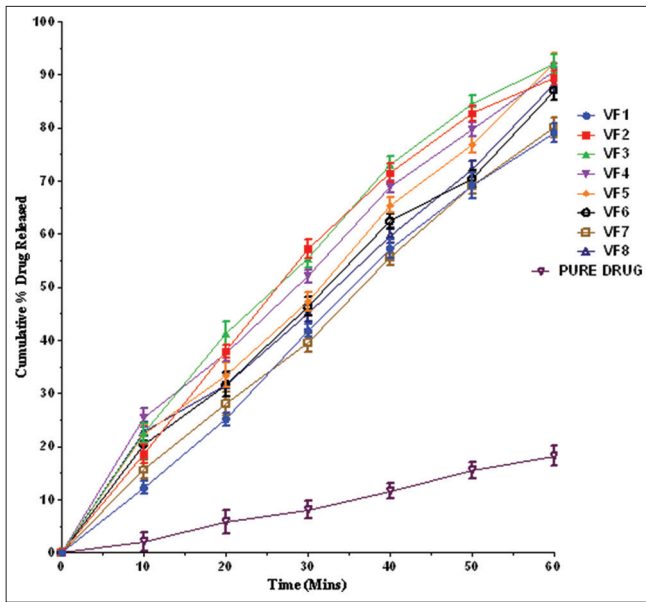


Figure 9: Cumulative% drug release profile of verapamil SNEDDS (VF1-VF8)

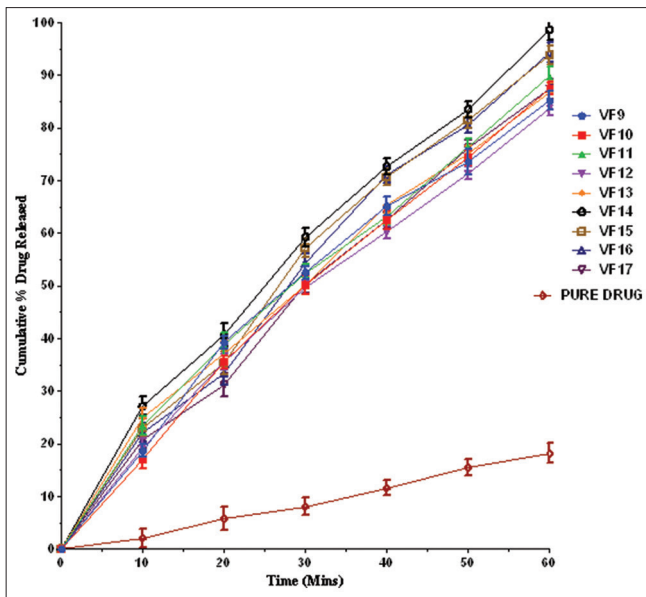


Figure 10: Cumulative% drug release profile of verapamil SNEDDS (VF9-VF17)

The mean values of *z* for three independent samples were documented.^[8]

Entrapment efficiency

A weighed quantity of SNEDDS was added to 100 mL of phosphate buffer of pH 7.4. The resulting mixture was kept for 24 h at dark place. Then, the solution was filtered through membrane filter of 0.45 μm pore size and 1 mL of this solution was diluted to 10 mL using phosphate buffer of pH 7.4. After further suitable dilution, the samples were analyzed by UV for the drug content at 278 nm.^[9]

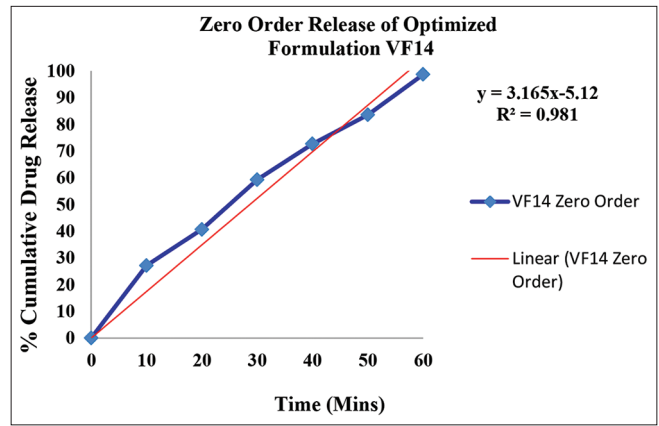


Figure 11: Zero-order plots for the optimized formulation (VF14) of verapamil SNEDDS

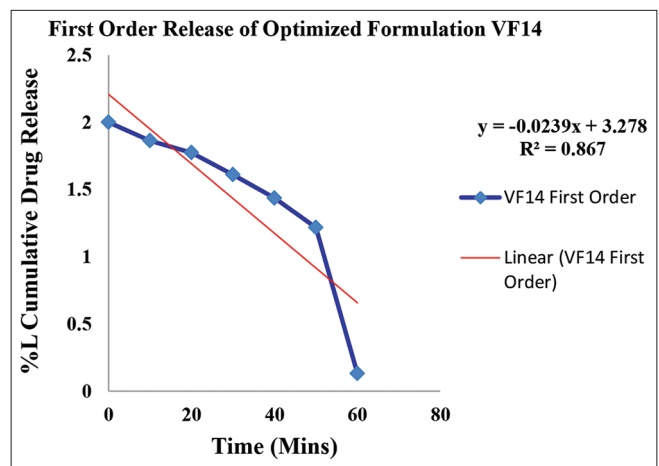


Figure 12: First-order plots for the optimized formulation (VF14) of verapamil SNEDDS

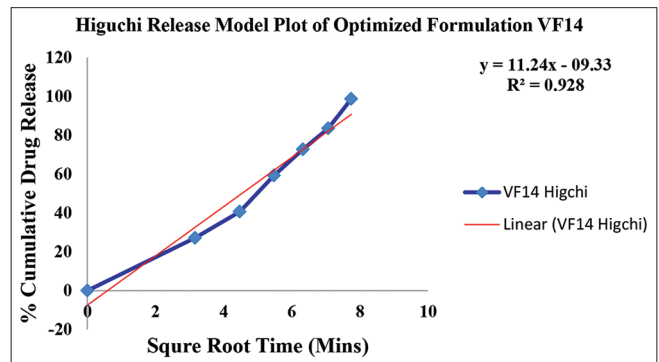


Figure 13: Higuchi plots for the optimized formulation (VF14) of verapamil SNEDDS

The drug entrapment efficiency was determined using the relationship

$$\text{Drug entrapment efficiency} = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \times 100$$

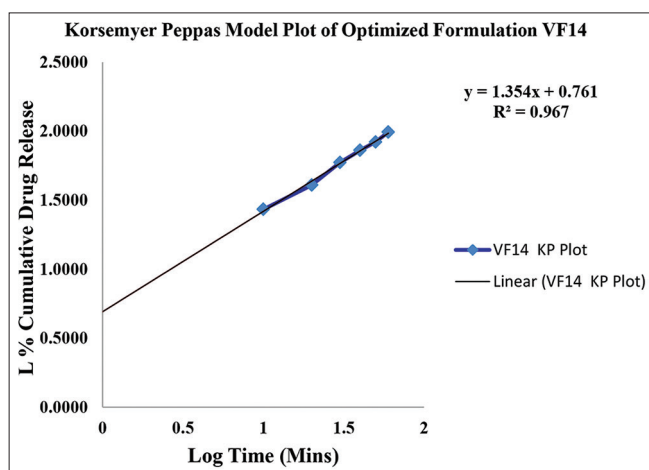


Figure 14: Korsmeyer-Peppas plots for the optimized formulation (VF14) of verapamil SNEDDS

Percentage drug content

All the experimental design batches of verapamil-loaded SNEDDS were subjected to assay analysis to determine their percentage drug content. Accurately weighed samples were dissolved individually in 10 mL of methanol and stirred by vortex mixer for a period of 10 min. Each of the solutions was filtered, using membrane filter (0.45 mm) and the drug content of each filtrate was estimated spectrophotometrically against blank at 278 nm. The study was repeated for three independent samples to confirm reproducibility of the results.^[10]

In vitro release studies of verapamil SNEDDS

Drug release tests on each batch of the SNEDDS were carried out using a USP I dissolution rate test apparatus at a stirring speed of 50 rpm and temperature of $37 \pm 0.5^\circ\text{C}$. An amount of the SNEDDS equivalent to 40mg of drug was filled in a hard gelatin capsule (Size no.0) and was placed in the dissolution medium containing 900 mL of phosphate buffer pH 7.4. A 5 mL quantity of the dissolution medium was sampled at predetermined time intervals of every 10 min up to 60 min and fresh dissolution medium was simultaneously used to replenish the dissolution medium on each occasion to keep the volume constant. The sample was filtered through filter disk and the filtrate was diluted with fresh dissolution medium if necessary. The samples were analyzed using RP-HPLC UV detector at 278 nm.^[11]

Pseudo ternary phase diagram study

On the basis of the solubility study of drug, oil, surfactant, and cosurfactant were selected. Distilled water was used as an aqueous phase for phase diagram study. Surfactant and cosurfactant (Smix) were mixed in different weights ratios (1:1, 1:2, 1:3, 2:1, 3:1, and 4:1). These S mix ratios were chosen in increasing concentration of surfactant with respect

to cosurfactant, and increasing concentration of cosurfactant with respect to surfactant. For each phase diagram, oil and specific Smix ratio were mixed in different ratios. Pseudo ternary phase diagrams were developed using aqueous titration method. Slow titration with distilled water was done with each weight ratio of oil and Smix and visual observation was carried out for transparent and easily flowable O/W emulsion. The results obtained were marked on a pseudo-three-component phase diagram with one axis representing oil phase, other representing mixture of surfactant and cosurfactant at fixed weight ratios, and third representing aqueous phase.^[12]

Experimental design

Box–Behnken experiment design

A three-factor and three-level Box–Behnken Design was used to explore and optimize the main effects, interaction effects, and quadratic effects of the formulation ingredients on the performance of the liquid SNEDDS. This design is suitable for exploring quadratic response surfaces and constructing second-order polynomial models. Tables 1-5 shows 17 randomized experimental runs for the selected independent variables, including five replicates at the center point (asterisk-marked) generated from a three factor, three-level BBD, and their corresponding responses. Five replicates at the center point were taken in this study for more uniform estimate of the prediction variance over the entire design space. The amount of drug added to the formulation was kept constant. Based on the boundary of the self-nano-emulsification domain in the ternary phase diagram, three levels of independent or formulation variables (amount of oil, surfactant, and cosurfactant) were identified: Low (coded as -1), middle (coded as 0), and high (coded as +1), as shown in Tables 1-5. The range for each independent variable was selected from the ternary phase diagram: that is, the amount of Captex 355 (oil, X_1) was 10–30%, the amount of acrysol K140 (surfactant, X_2) was 20–40%, and the amount of PEG 400 (cosurfactant, X_3) was 10–30% (Tables 1-5).

The significant response factors used to assess the quality of the SNEDDS formulation, including droplet size (Y1), ZP (Y2), and cumulative percentage of drug released (Y3), were determined [Table 1].^[13]

Selection of formulations from phase diagram

A pseudo ternary phase diagram of the investigated quaternary system water/captex 355/Acrysol K140/PEG 400 is presented. Formation of SNEDDS systems (the shaded area) was observed at room temperature. Phase behavior investigations of this system demonstrated the suitable approach of determining the water phase, oil phase, surfactant concentration, and cosurfactant concentration with which the transparent, 1-phase low-viscous SNEDDS system

Table 1: List of dependent and independent variables in in Box–Behnken design

Independent variables			Levels		
Variable	Name	Units	Low (-1)	Middle (0)	High (+1)
A	Amount of Captex 355	mg	10	20	30
B	Amount of Acrysol K140	mg	20	30	40
C	Amount of PEG 400	mg	10	20	30
Dependent variable			Goal		
Y1	Droplet size	nm	Minimize		
Y2	Zeta Potential	mV	Minimize		
Y3	Drug release after 60 min	%	Maximize		

Table 2: Box–Behnken design with observed responses

Run	Amount of captex 355 (mg)	Amount of acrysol K140 (mg)	Amount of PEG 400 (mg)	Droplet size (nm)	Zeta potential	Drug release after 60 min (%)
1	10	20	20	39.2	18.7	79.14
2	20	20	20	46.1	19.6	89.44
3	30	40	30	62.9	22.3	92.13
4	20	40	20	79.3	16.8	90.78
5	10	30	10	35.7	18.6	92.23
6	10	20	10	63.9	23.3	87.12
7	10	30	30	72.4	21.9	80.13
8	30	30	30	34.6	16.7	88.35
9	20	20	10	42.4	23.5	85.16
10	30	40	10	76.1	15.2	87.59
11	20	20	30	48.0	17.5	89.82
12	20	20	20	88.7	19.2	83.67
13	30	30	20	51.9	16.8	86.72
14	10	40	30	75.3	24.4	98.65
15	30	40	20	66.1	21.8	93.88
16	20	30	10	85.5	17.9	94.38
17	10	30	20	77.3	20.3	87.43

Table 3: ANOVA of the quadratic model for the response droplet size (Y1)

Source of variations	Sum of squares	Degree of freedom	Mean squares	F-value	P-value Prob>F	R ²
Model	4439.15	9	492.88	0.0263	<0.05	0.9995
A-amount of captex 355	23.76	1	23.76	0.0188	<0.05	
B-amount of acrysol K140	1389.61	1	1389.61	0.0245	<0.05	
C-amount of PEG 400	255.15	1	255.15	0.0123	<0.05	
AB	317.90	1	317.90	0.0171	<0.05	
AC	249.80	1	249.80	0.0435	<0.05	
BC	0.79	1	0.79	0.0210	<0.05	
Residual	2837.29	7	405.33			
Lack of fit	445.62	3	148.21	0.0193	<0.05	

was formed. The phase study revealed that the maximum proportion of oil was incorporated in SNEDDS systems when

the surfactant/cosurfactant ratio was 1:1. From a formulation viewpoint, the increased oil content in SNEDDS may provide

Table 4: ANOVA of the quadratic model for the response zeta potential (Y2)

Source of variations	Sum of squares	Degree of freedom	Mean squares	F-value	P-value Prob>F	R ²
Model	567.76	6	94.79	0.0128	<0.05	0.9992
A-amount of captex 355	63.95	1	63.95	0.0156	<0.05	
B-amount of acrysol K140	0.12	1	0.182	0.0349	<0.05	
C-amount of PEG 400	234.20	1	234.20	0.0277	<0.05	
AB	85.10	1	85.10	0.0072	<0.05	
AC	55.23	1	55.23	0.0311	<0.05	
BC	83.32	1	83.32	0.0367	<0.05	
Residual	195.24	10	19.12			
Lack of fit	322.51	6	53.42	0.0458	<0.05	

Table 5: ANOVA of the quadratic model for the response cumulative percent drug release (Y3)

Source of variations	Sum of squares	Degree of freedom	Mean squares	F-value	P-value Prob>F	R ²
Model	588.25	6	98.71	0.0211	<0.05	0.9995
A-amount of captex 355	37.71	1	37.71	0.0296	<0.05	
B-amount of acrysol K140	64.11	1	64.11	0.0222	<0.05	
C-amount of PEG 400	6.86	1	6.86	0.0315	<0.05	
AB	89.72	1	89.72	0.0196	<0.05	
AC	52.76	1	52.76	0.0121	<0.05	
BC	38.09	1	38.09	0.0343	<0.05	
Residual	296.02	10	29.60			
Lack of fit	345.17	6	57.20	0.0288	<0.05	

a greater opportunity for the solubilization of verapamil. Moreover, when the composition (%w/w) of surfactant mixture (Smix) in a SNEDDS preparation was <50%, the formulation was less viscous.

The optimum formulation of SNEDDS contained captex 355 (23.41%), Smix (51.62%), and water (11.58%). It can be seen that the largest SNEDDS region is seen when the combination of surfactant and cosurfactant is used. When a cosurfactant is added to the system, it further lowers the interfacial tension between the oil and water interface and also influences the interfacial film curvature, which there by readily deforms around oil droplets. Ternary phase diagrams were constructed to identify the self-emulsifying regions and also to establish the optimum concentrations of oil, surfactant, and cosurfactant. From the phase diagrams, it was observed that as increasing the concentration of surfactant increased the self-emulsifying region. Emulsification region decreased with increasing the concentration of co-surfactant.

Design of experiments

Statistical analysis of the designed experiment

A series of experiments was performed based on the experimental runs generated from a three-factor, three-level

Box–Behnken design. The experimental matrix from the randomized runs for the independent variables and responses observed is shown in Tables 1-5. The range of droplet size (Y1) for all batches was 33.9–89.3 nm. Similarly, the range for ZP (Y2) was 15.2–23.8 mV and the range for cumulative percentage of drug released in 60 min (Y3) was 80.14–98.22%. All responses were fitted to a second quadratic model and the adequacy of this model was verified by ANOVA, tests provided by Design-Expert software. All three responses were individually fitted to a second-order quadratic model and each obtained model was validated by ANOVA. For all the responses, the second-order quadratic model generated the highest F value, so it was identified as the fitting model. Moreover, the lack of fit test is another good statistical parameter for checking the fitness of the model. It compares the residual error with the pure error from the replicated design points (five center points in this study). A model with a significant lack-of-fit (Prob>F value 0.12 or smaller) lacks prediction efficiency, so a non-significant lack of fit value in the model is highly desirable. All of the responses fitted in the quadratic model showed a significant lack-of-fit F value ($P > 0.5$), proving the adequacy of the model fit. Furthermore, the multiple regression analysis for the second-order quadratic model is shown as R² value, which signifies the measure of the amount of variation around the mean explained by the model (Figures 1- 8).

Optimization by desirability function

An optimization process was undertaken with desirability function to optimize the three responses simultaneously. The responses: droplet size (Y1), ZP (Y2), and cumulative percentage of drug released in 60 min (Y3) were transformed into the desirability scale, respectively. Among them, Y1 and Y2 had to be minimized, while Y3 had to be maximized. For individual desirability function, Y_{\max} and Y_{\min} were taken as the highest objective function (D) was calculated by Equation (3) for each response. Finally, the global desirability value was calculated by combining the individual desirability function as the geometric mean by an extensive grid search and feasibility search over the domain by the Design-Expert software. The maximum function value was obtained at X1:10, X2:40, and X3:30. To confirm the model adequacy for prediction, three batches of formulations under the optimum composition were prepared, and the three responses were evaluated for each formulation. The results are shown in Table. The model was proven to be validated since a fine agreement existed between the predicted and observed results. It can be seen that the experimental values were in very close agreement with the predicted values, indicating the success of the Box–Behnken design combined with a desirability function for the evaluation and optimization of SNEEDS formulations.

Kinetic analysis of verapamil release data

Release kinetics

From the above results, it is apparent that the regression coefficient value closer to unity in case of zero-order plot, that is, 0.981 indicates that the drug release follows a zero-order mechanism. This data indicates a lesser amount of linearity when plotted by the first order equation. Hence, it can be concluded that the major mechanism of drug release follows zero-order kinetics (Figures 9-14).

Further, the translation of the data from the dissolution studies suggested possibility of understanding the mechanism of drug release by configuring the data in to various mathematical modeling such as Higuchi and Korsmeyer-Peppas plots. Further, the n value obtained from the Korsmeyer-Peppas plots, that is, 0.967 indicating non-Fickian (anomalous) transport; thus, it projected that delivered its active ingredient by coupled diffusion and erosion and also suggest that the drug release from SNEEDS was super case-II transport system release rate function was t^{n-1} .

Stability study

There were no physical changes in appearance and flexibility. After subjecting the optimized formulation (VF14) to the accelerated stability studies, the results were shown that there were no major changes in drug entrapment efficiency, *in vitro* drug release, and content uniformity. Hence, the formulation was found to be stable.

CONCLUSION

In this study, SNEEDS of verapamil was prepared and evaluated. The optimized formulation (VF14) consisting of captex 355 (23.41%), Smix (51.62%), and water (11.58%) exhibited faster release profiles with a rapid rate of emulsification. The optimized SNEEDS formulation of verapamil showed a significant increase in the dissolution rate and oral absorption compared with the aqueous drug suspension. Thus, SNEEDS can be regarded as a novel and commercially feasible alternative to the current Verapamil formulations.

DECLARATIONS

Ethics approval and consent to participation

Not applicable.

Consent for publication

No conflicts of interest among the authors.

Availability of data and material

All required data are available.

ACKNOWLEDGMENTS

Authors are thankful to the management of Srikrupa Institute of Pharmaceutical sciences for providing the laboratory facilities to carry out this research work.

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Source of Support: Nil. **Conflicts of Interest:** None declared.