Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

Available online at www.ijpsdronline.com

Research Article

Development and Evaluation of Manidipine Loaded Self-Nanoemulsifying Drug Delivery System by Box-Behnken Design

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ARTICLE INFO

Article history:

Received: 27 April, 2021

Revised: 11 May, 2021

Accepted: 17 May, 2021

Published: 30 May, 2021

Keywords:

Box-Behnken design,
Hypertension,
Manidipine,
Solubility,
SNEDDS.

DOI:

10.25004/IJPSDR.2021.130315

ABSTRACT

The current study aims to formulate an anti-hypertensive drug manidipine self-nanoemulsifying drug delivery system (SNEDDS) employing different novel polymers to enhance solubility and drug release manidipine. The optimal concentration of excipients chosen based on solubility study further confirmed by self-emulsification region of pseudo ternary phase diagram. Manidipine SNEDDS optimized employing box-behnken design (BBD) through the study of factors - the amount of capryol 90(A), cremophor RH40 (B) and triacetin (C) and responses -droplet size (Y1), zeta potential (Y2), and cumulative percentage of drug release after 60 minutes (Y3). All formulations were evaluated for particle size, zeta potential, polydispersity index, entrapment efficiency, drug content, and in-vitro drug release. The optimized formulation was characterized for FTIR, SEM, and stability studies. The study indicates that manidipine optimized formulation MF11 comprising of capryol 90 (40.0%), cremophor RH40 (10.0%) and triacetin (30.0%) exhibited minimum droplet size (76.5 ± 2.87), best zeta potential (-24.7 ± 1.31mV) and entrapment efficiency (98.23 ± 1.74%) content uniformity (99.12 ± 1.28%) maximum drug release (98.79 ± 1.68%). The fourier transform infrared spectroscopy (FTIR) studies of MF11 indicated no significant interaction amid the drug and formulation excipients. The scanning electron microscopy (SEM) data revealed that particle size is in the nanometer range with a zeta potential value >5 mV indicating higher absorption and stability. Accelerated stability studies indicated the formulation to be stable for 3 months. Hence the results revealed that application of SNEDDS formulation technique for manidipine increased solubility and drug release.

Introduction

Manidipine is used as an anti-hypertensive. Manidipine binds to voltage-dependent calcium channels on smooth muscle cells and dissociates them, thus blocking the entrance of extracellular calcium into the cell hence preventing this contraction. This produces vasodilation which decreases blood pressure.[1] Class II drug in BCS classification has lesser water solubility and reduced bio-availability (50%). Investigation of potential formulation techniques for enhancing the bioavailability of manidipine is a matter of importance.[2]

Various solubility enhancement techniques are employed to enhance the drug solubility and release characteristics, the most acceptable being SNEDDS. It is a drug formulation system based on lipids in which drug is entrapped in a lipid stabilized by surfactants that spontaneously form oil in water emulsion on coming in contact with the body fluids. The surfactants decrease the interfacial tension between the fluids and lipid, enabling the drug to get disperse easily and available for absorption, thus enhancing bioavailability.[3]

In the recent past, experiments (DoE) were widely applied to understand the effect of factors on responses of

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

pharmaceutical products and formulation methods. In this approach, the factors are methodically varied to establish their effects on responses that permit the determination of most significant input factors, resulting in optimized output responses. The BBD deals with the influence of independent variables on dependent factors. BBD allows modeling first and second-order response surfaces in cost effective way.[4]

The present work is focused on formulation and evaluation of manidipine SNEDDS using BBD for enhanced solubility and drug dissolution.

Materials

Manidipine gifted from Aurobindo Pharma Ltd, Hyderabad. Capmul MCM, Captex 355, Capmul PG8, Capryol 90, Imwitor 742, IPM, Labrafil M2, Labrafac CC, Labrafac Lipophile WL 1349, Maisine 35-1, Miglyol 812, Paceol, Sefsol 218, Olive oil, Oleic acid and Castor oil, Acrysol K140, Acrysol EL135, Acconon E, Acconon CC400, Acconon Sorb20, Capmul GMO 50, Caprol PGE 860, Caprol ET, Cremophor EL, Cremophor RH40, Gelucire 44/14, Labrasol, Solutol HS15, Tween 80, Tween 20 and Triton-9100, Capmul MCMC8, Lauroglycol 90, PEG 400, PG, EG, PlurolOleique CC497, Triacetin, Transcutol P, Propylene Glycol procured from Gattefosse, France.

Selection of SNEDDS Components

Selection of Oil (Solubility Studies)

The solubility's of Manidipine were measured in numerous oils (Capmul MCM, Captex 355, Capmul PG8, Capryol 90, Imwitor 742, IPM, Labrafil M2, Labrafac CC, Labrafac Lipophile WL 1349, Maisine 35-1, Miglyol 812, Paceol, Sefsol 218, Olive oil, Oleic acid, and Castor oil) individually by shake flask method at a constant temperature. An excess amount of drug was introduced into 2 mL of each excipient, and these mixtures were sealed in glass vials. Each of the samples was subjected to vortex mixing on a vortexer for 5 min to facilitate initial mixing. Further, vials were charged on an environmental shaker bath for 72 hours at 37 °C with 300 rpm speed. After equilibrium for an additional 72 hours at 25°C temperature, each vial was centrifuged at 10000 rpm for 10 minutes using a centrifuge. The supernatant of each sample was filtered through a membrane filter (0.45 mm) to remove any undissolved drug if present. The amount of drug in all samples was determined by their subsequent dilution with suitable solvent using double beam UV Visible spectrophotometer against blank at 228 nm. The study was repeated in triplicate and their mean values were recorded.[5]

Selection of Surfactant (Emulsification Study)

Sixteen non-ionic surfactants (Acrysol K140, Acrysol EL135, Acconon E, Acconon CC400, Acconon Sorb20, Capmul GMO 50, Caprol PGE 860, Caprol ET, Cremophor EL, Cremophor RH40, Gelucire 44/14, Labrasol, Solutol HS15, Tween 80, Tween 20 and Triton-9100) were screened to evaluate their propensity to emulsify optimized oil phase. Briefly, 300 ml of selected surfactant was added to 300 mL of the selected oil phase. The mixture was then vortexed for 60 seconds to facilitate the mixing of oil and surfactant. One hundred milligrams of this isotropic system were weighed accurately and diluted to 25 mL of distilled water to yield a fine emulsion. Further, all these samples of emulsions were allowed to stand for 2 hours and their percentage transmittance (%T) were evaluated individually at 228 nm by double beam UV spectrophotometer against distilled water as blank. The resultant emulsions were also evaluated for their visually transparency and phase separation after 24 hours storage at 25°C temperature. The study was performed in triplicates and the average values were recorded [6].

Selection of Co surfactant (Emulsification Study)

The co-surfactants can improve the nano emulsification efficiency. Eight co-surfactants [Capmul MCMC8, Lauroglycol 90, PEG 400, PG, EG, Plurol Oleique CC497, Triacetin, Transcutol P, Propylene Glycol] were screened for their potential to assist previously selected surfactant in terms of emulsification of respective oil phase. The screening of co-surfactant was done by following constraints based on their role in final formulations. First, the relative effectiveness of co-surfactants was evaluated by adding 200 mL of surfactant with 100 mL of co-surfactant, and to this 300 mL of oil was added and vortexed to homogenize the mixture. The formed emulsions were then evaluated for their transmittance at 228 nm by UV spectrophotometer, using double-distilled water as blank. The study was performed in triplicates and the average values were noted.[7]

Pseudo Ternary Phase Diagram Study

Based on the solubility study of drug, oil, surfactant, and co-surfactant were selected. Distilled water was used as an aqueous phase for the phase diagram study. Surfactant and co-surfactant (S_{mix}) were mixed in different weight ratios (1:1, 1:2, 1:3, 2:1, 3:1 and 4:1). These Smix ratios were chosen to increase surfactant concentration concerning co-surfactant and increase the concentration of co-surfactant concerning surfactant. For each phase diagram, oil and specific S_{mix} ratio were mixed in different ratios (0.5:9.5, 1:9, 1.5:8.5, 2:8, 2.5:7.5, 3:7, 3.5:6.5, 4:6, 4.5:5.5, 5:5, 5.5:4.5, 6:4, 6.5:3.5, 7:3, 7.5:2.5, 8:2, 8.5:1.5, 9:1 and 9.5:0.5). 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, the other representing mixture of surfactant

and co-surfactant at fixed weight ratios, and the third representing the aqueous phase.[8]

Preparation of Manidipine Loaded SNEDDS

The Manidipine loaded SNEDDS were prepared by mixing oil phase (Capryol 90), surfactant (cremophor RH40), and co-surfactant (Triacetin) and warming it at 40°C, then Manidipine was added to the mixture and vortexed to facilitate the uniform dispersion of Manidipine. The mixture was then allowed to equilibrate at room temperature. According to the experimental design, seventeen such experiments were carried out with varying oil, surfactant, and cosurfactant concentrations, with the final Manidipine loading equivalent to 10 mg/gm. Manidipine (10 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 were added surfactant and co-surfactant and sonicated for 60 minutes. The prepared Manidipine-loaded SNEDDS were filled into size 0 gelatin capsule shells.[9]

Experimental Design

Box–Behnken Experiment Design (BBD)

A 3^3 BBD was employed for optimizing the main, interaction, and quadratic effects of formulation components on characteristics of SNEDDS. Seventeen experiments run randomly for chosen independent variables that include 5 repetitions at the center (asterisk-marked) obtained from 3 factors, 3-level BBD, and subsequent responses noted. The variables that were chosen as dependent and independent are specified in Tables 1 and 2.

The BBD matrix obtained using Design Expert® software (Version7.0, Stat-Ease Inc., Silicon Valley, CA, USA), the second-order quadratic equations are:

$$Y = \beta_1 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_1 X_2 + \beta_5 X_2 X_3 + \beta_6 X_1 X_3 + \beta_7 X_1^2 + \beta_8 X_2^2 + \beta_9 X_3^2$$

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 Capryol 90	Mg	20	30	40
B	Amount of Cremophor RH 40	Mg	10	20	30
C	Amount of Triacetin	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 Capryol 90(mg)*	*Amount of Cremophor RH 40(mg)*	*Amount of Triacetin (mg)*	*Droplet size (nm)*	*Zeta Potential (-mV)*	*Drug release after 60 min (%)*
1	20	10	10	93.2	29.5	92.45
2	40	10	20	81.5	26.6	86.26
3	20	30	20	80.9	27.3	85.53
4	20	30	10	83.8	29.8	90.48
5	20	20	10	104.1	26.6	93.38
6	30	20	10	162.4	26.3	92.55
7	20	20	30	171.5	28.9	91.53
8	20	10	30	128.8	26.7	85.38
9	30	10	10	144.2	23.5	92.34
10	30	30	30	168.1	27.2	88.29
11	40	10	30	76.5	24.7	98.79
12	40	30	30	94.6	29.1	94.21
13	30	20	20	153.3	27.8	86.17
14	30	10	20	82.5	26.2	92.16
15	40	20	30	85.3	25.1	83.46
16	30	30	20	86.8	26.3	87.44
17	40	20	10	83.6	28.1	85.24

Y - Level of the measured response

β_0 – intercept

β_1 to β_9 - regression coefficient

X_1, X_2, and X_3 - main effects

X_1X_2, X_2X_3, and X_1X_3 - interaction between the main effects

X_1^2, X_2^2 and X_3^2 - quadratic terms of independent variables.

Optimization using the Desirability Function

In the present study, all three responses were simultaneously optimized by a desirability function that uses the numerical optimization method introduced by Derringer and Suich [10] in the Design-Expert software (Version8.0, Stat-Ease Inc., Silicon Valley, CA, USA).

Characterization of SNEDDS

Developed Manidipine 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 seventeen different liquid SNEDDS formulations (10 mg), each containing 5% Manidipine, were prepared. Then, 40 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 304 nm, 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 were derived from cumulated analysis by auto measure software (Malvern Instruments).[11]

Zeta Potential

The zeta potential (z) values were evaluated for all experimental design batches of Manidipine-loaded SNEDDS by determining the particle electrophoretic mobility using a 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. The mean values of z for three independent samples were documented.[12]

Entrapment Efficiency

A weighed quantity of SNEDDS was added to 100mL of phosphate buffer of pH 7.4. The resulting mixture was kept for 24 hours in a dark place. Then the solution was filtered through a membrane filter of 0.45 µm pore size, and 1mLof this solution was diluted to 10 mL using phosphate buffer of pH 7.4. After further suitable dilution, the samples were analyzed by HPLC for the drug content at 228 nm.[13]

The drug entrapment efficiency was determined using the relationship

Drug entrapment efficiency = [Experimental drug content x 100]/Theoretical drug content.

Percentage Drug Content

All the experimental design batches of Manidipine-loaded SNEDDS were subjected to assay analysis in order to determine their percentage drug content. Accurately weighed samples were dissolved individually in 10 mL of methanol and stirred by vortex mixer for 10 minutes. Each solution was filtered using a membrane filter (0.45 mm), and the drug content of each filtrate was estimated spectrophotometrically against blank at 228 nm. The study was repeated for three independent samples to confirm the results' reproducibility.[14]

In-vitro Release Studies of Manidipine 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 ± 0.5ºC. An amount of the SNEDDS equivalent to 40 mg 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 to 60 minutes, and a fresh dissolution medium was simultaneously used to replenish the dissolution medium on each occasion to keep the volume constant. The sample was filtered through a filter disc, and the filtrate was diluted with a fresh dissolution medium if necessary. The samples were analyzed using RP-HPLC UV detector at 228 nm.[15]

Results

Percentage Drug Content and Entrapment Efficiency

The %drug content of all manidipine SNEDDS from 96.21 ± 0.35 to 99.12 ± 1.28%, and the entrapment efficiency varied from 94.16 ± 0.064 to 98.23 ± 1.74%, with the maximum value recorded for MF11.

Selection of Formulations from Phase Diagram

The phase study revealed that the maximum proportion of oil was incorporated in SNEDDS systems when the surfactant/co-surfactant ratio was 1:1. From a formulation

viewpoint, the increased oil content in SNEDDS may provide a greater opportunity for the solubilization of Manidipine. Moreover, when the composition (% w/w) of surfactant mixture (S_{mix}) in a SNEDDS preparation was <50%, the formulation was less viscous.

The optimum formulation of SNEDDS contained capryol 90 (9.43%), Smix (56.32%), and water (38.89%). It can be seen that the largest SNEDDS region is seen when the combination of surfactant and co-surfactant is used. When a co-surfactant is added to the system, it further lowers the interfacial tension between the oil and water interface and influences the interfacial film curvature, which readily deforms around oil droplets. (Figs. 1 to 6)

Design of Experiment

About 17 experiments were performed according to experimental runs generated by 3^3 Box– Behnken design. All responses fitted into second-order quadratic equations, and the competence of the model validated by ANOVA tests provided by Design-Expert software (Table 3).

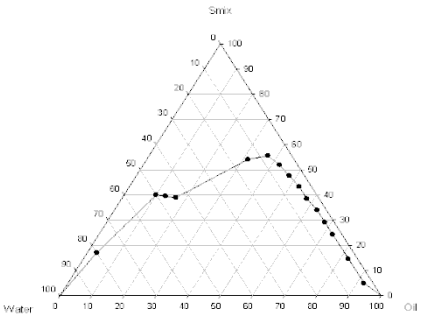

Fig. 1: Pseudo tertiary graph of S_{mix} ratio1:1

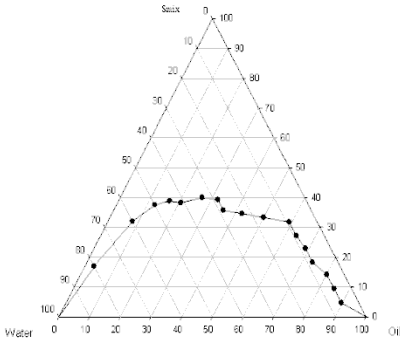

Fig. 2: Pseudo tertiary graph of S_{mix} ratio1:2

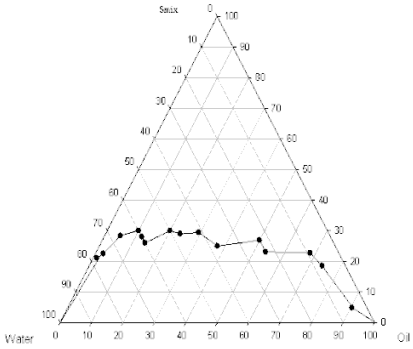

Fig. 3: Pseudo tertiary graph of S_{mix} ratio1:3

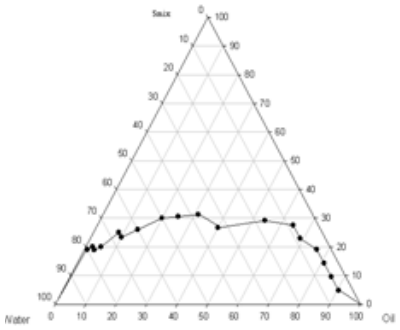

Fig. 4: Pseudo tertiary graph of S_{mix} ratio2:1

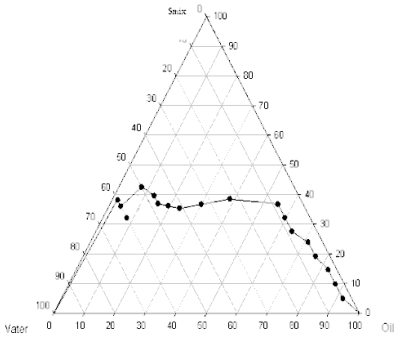

Fig. 5: Pseudo tertiary graph of S_{mix} ratio3:1

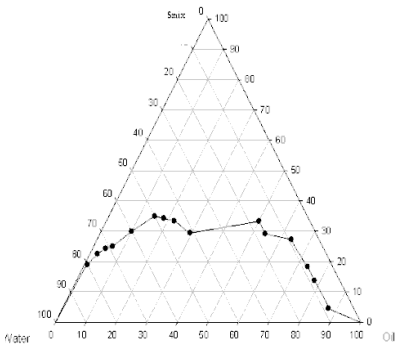

Fig. 6: Pseudo tertiary graph of S_{mix} ratio4:1

Table 3: Regression equations of the fitted models

Response	*Equation*
Droplet size (Y1)	$67.18+12.74X1-15.58X2-1.39X3-0.19X^2_1 + 0.17X_1X_3+21.47\ X^2_2-1.45\ X_2X_3+1.05\ X^2_3$
Zeta Potential(Y2)	$18.65+06.21X1+04.66X2+3.89X3+0.22X^2_1 - 0.13X_1X_3 -06.54\ X^2_2-3.43\ X_2X_3-2.64\ X^2_3$
% Cumulative drug released(Y3)	$91.78-4.23X1+07.96X2-13.29X3+0.57X^2_1-14.47X_1X_3+05.15\ X^2_2-13.43\ X_2X_3+1.28\ X^2_3$

Where Y_1, Y_2 and Y_3 are the predicted response and X_1, X_2 and $_{X3}$ are the coded values of the test variables in respective concentrations

Response Surface Analysis

Stat-Ease Design-Expert ® software V8.0 was utilized for analyzing data, to get regression equation, regression coefficient, and analysis of variance (ANOVA).

Droplet Size

The particle size of the SNEDDS was found to be in the range of 76.5–171.5 nm. The mathematical model generated for droplet size (Y1) was significant, with an F-value of 4156.72 implies the model is significant. The respective contour plots are shown in Figs. 7 and 8. The increase in the droplet size with a concomitant increase in the amount of oil (X1) or decrease in the amount of surfactant (X2) and vice versa has been reported in many papers about SNEDDS. This phenomenon may be explained by the fact that higher proportion of surfactant (with simultaneously lower oil amount) may provide closely packed interfacial surfactant film, thereby stabilizing the oil droplets. This may also explain the significant interaction between the amount of oil and surfactant.

Zeta Potential

The zeta potential of the nanoparticles was found to be in the range of 24.7-29.8 as shown in Table 3. The quadratic model generated revealed that the amount of cremophor RH40 and amount of Triacetin have a significant influence on the zeta potential. The theoretical (predicted) values and the observed values were in reasonably good agreement, as seen. The mathematical model generated for zeta potential (Y2) was significant, with an F-value of 0.168 implies the model is significant. The respective contour plots are shown in Figs. 9 and 10.

Cumulative Percent Drug Released

The Cumulative percent drug release in 60 min from the nano-formulations was found to be in the range of 83.46–98.79 %, as shown in respective contour plots, as shown in Figs. 11 and 12. The amount of surfactant was

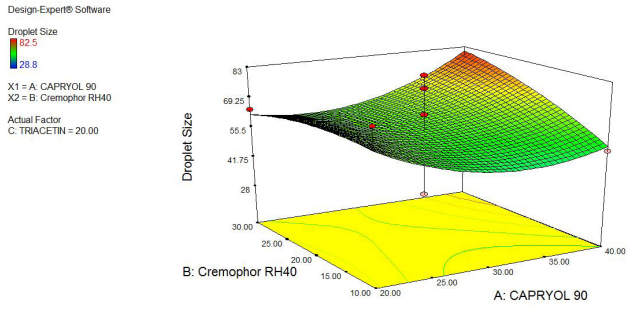

Fig. 7: Response 3D surface plot showing the influence of amount of Capryol 90 and amount of cremophor RH40 on droplet size fixed level of C

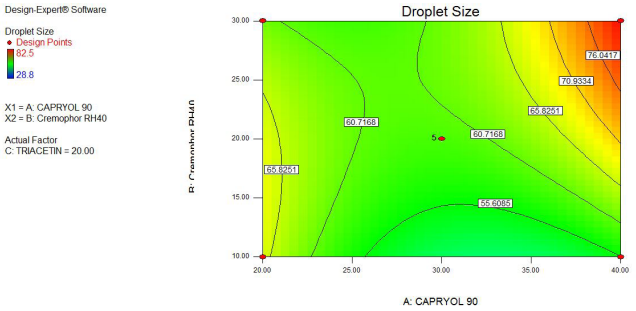

Fig. 8: Contour plot showing the influence of amount of Capryol 90 and amount of cremophorRH40 on droplet size fixed level of C

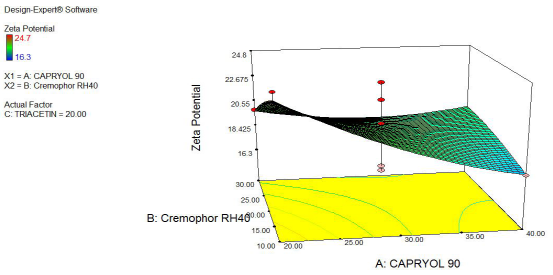

Fig. 9: Response 3D surface plot showing the influence of amount of Capryol 90 and amount of cremophor RH40 on Zeta Potential level of C

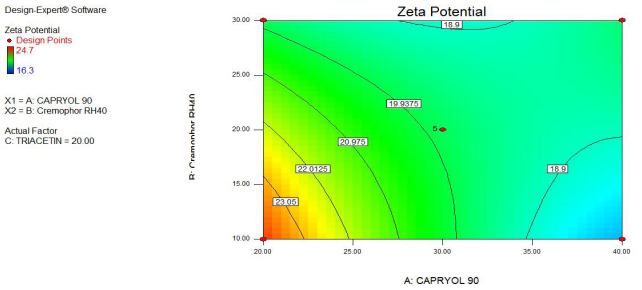

Fig. 10: Contour plot showing the influence of amount of Capryol 90 and amount of cremophor RH40 on Zeta Potential level of C

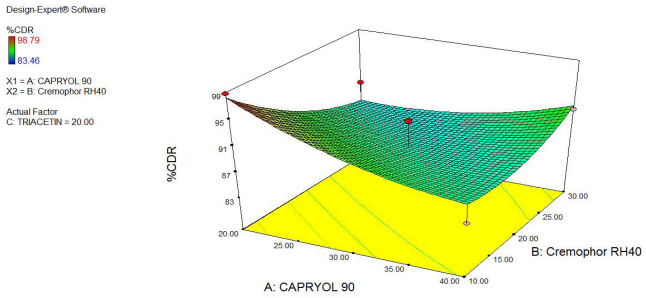

Fig. 11: Response 3D surface plot showing the influence of amount of capryol 90 and amount of cremophor RH40 on Cumulative % Drug Released level of C

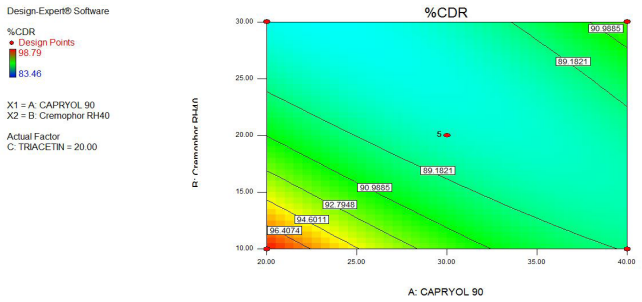

Fig. 12: Contour plot showing the influence of amount of capryol 90 and amount of cremophor RH40 on Cumulative % Drug Released of C

mainly responsible for the increase in the cumulative percentage of drug released from the formulation. The increase in cumulative drug release was mainly attributed to rapid self-emulsification of the formulations due to instantaneous dispersion in the medium after the dissolution of the capsule shell. As the amount of free energy required in forming an emulsion is very low, this results in the spontaneous formation of an oil-water interface. This increases the water penetration of oil droplets, resulting in disruption of the interface and thereby decreasing the droplet size and eventually increasing the release rate. It was also seen that the addition of the co-surfactant further improved the cumulative percentage of drug released. This phenomenon might be due to the penetration of the co-surfactant into the surfactant monolayer interface, which further enhances the self-emulsification performance of SNEDDS.

Optimization by Desirability Function

An optimization process was undertaken with a desirability function to optimize the three responses simultaneously. The responses: droplet size (Y1), zeta potential (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 the individual desirability function, Y_{max} and Y_{min} were taken as the highest objective function (D) was calculated by Equation (3) for each response. The maximum function value was obtained at X1:40, X2:10, and X3:30. 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 SNEDDS formulations (Table 4).

Characterization of SNEDDS

Developed Manidipine SNEDDSs were physicochemically evaluated in terms of refractive index (RI), percentage of transmittance (% T).

Refractive Index

Refractive index, being an optical property, is used to characterize the isotropic nature of nanoemulsion, which is to be produced from SNEDDS. The results of all three batches confirmed isotropic nature of the systems even after their transformation to nanoemulsions. The RI values of all formulations were in the range of 1.33–1.49.

Percentage Transmittance

A transmittance study was conducted to characterize the isotropic nature of SNEDDS, As a result, all the batches have shown nearly 100% transmittance for all batches.

In vitro Dissolution testing of Manidipine SNEDDS

The dissolution profiles of plain Manidipine and Manidipine SNEDDS formulation in simulated intestinal fluid (SIF, pH 6.8) media are presented in Figs. 13 and 14. In addition, the drug release profiles of formulation MF11 were analyzed. As shown in Fig. 14, more than 85% of drug was dissolved from MF11 after 60 min. However, the original Manidipine powder showed only approximately 0.7% dissolved after the same period (Fig. 15). This result suggested that the SNEDDS formulation significantly enhanced the dissolution of Manidipine. The enhanced dissolution may be due to the decrease in crystallinity and the increase in solubility of the drug. The increase in cumulative drug release is mainly attributed to rapid self-emulsification of the formulations due to instantaneous dispersion in the medium after the dissolution of the capsule shell. As the amount of free energy required in forming an emulsion is meager, this results in the spontaneous formation of an oil-water interface. This increases the water penetration of oil droplets, resulting in disruption of the interface

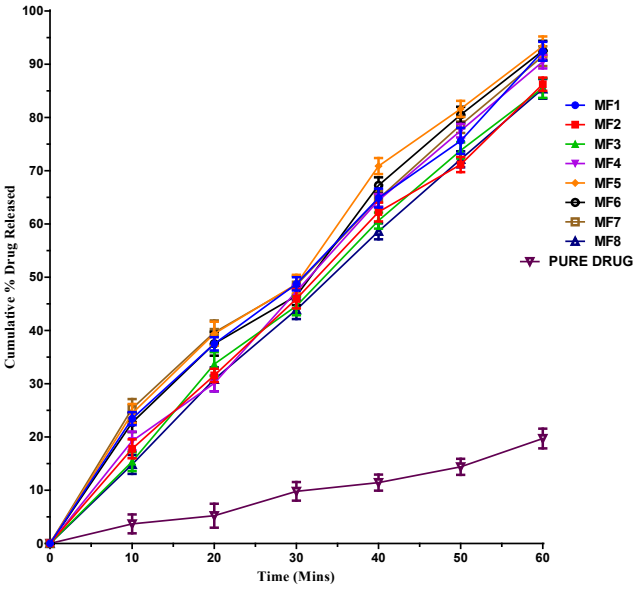

Fig. 13: Comparative dissolution profile of manidipine pure drug and manidipine SNEDDS formulation (MF1-MF8)

Table 4: Optimized values obtained by the constraints applies on Y1, Y2 and Y3

Predicted values					*Observed values*			
Independent variable	*Nominal values %*	*Droplet size (Y1) (nm)*	*Zeta Potential Mv (Y2)*	*%CDR (Y3)*	*Batch*	*Droplet size (Y1) (nm)*	*Zeta potential mV (Y2)*	*Percent drug release in 15 min (Y3)*
Amount of Capryol 90(A)	40	76.5	-24.7	98.79	1	67.8.1	-23.5	97.43
Amount of cremophor RH 40 (B)	10				2	75.9	-24.1	98.32
Amount of Triacetin (C)	30				3	76.1	-22.9	98.67

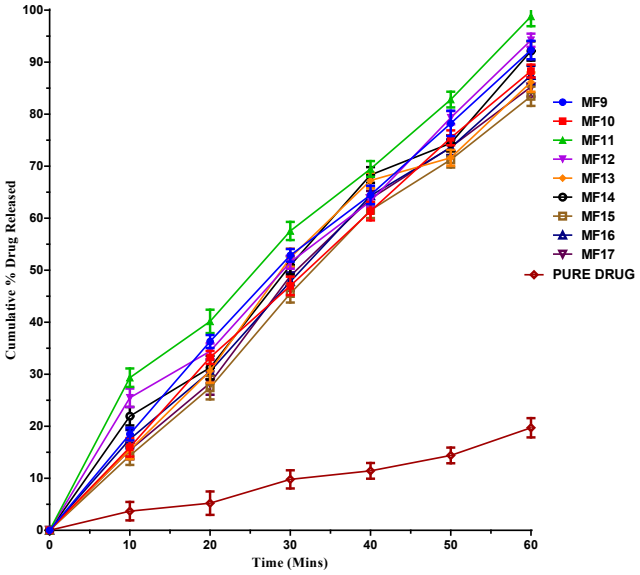

Fig. 14: Comparative dissolution profile of manidipine pure drug and manidipine SNEDDS formulation (MF9-MF17)

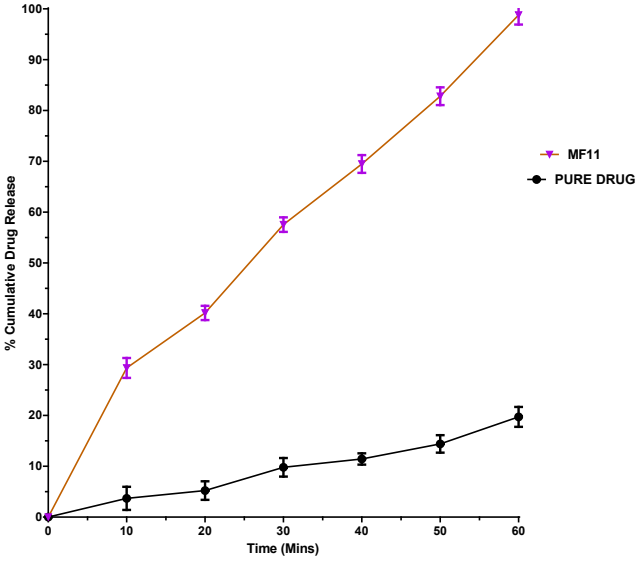

Fig. 15: Comparative *In vitro* study plot of optimized formulation MF11and Pure Drug.

and thereby decreasing the droplet size and eventually increasing the release rate. The formulation MF11 was selected as optimized formulation because it showed a maximize release.

Characterization of the Optimized SNEDDS Manidipine Formulation

Fourier Transform Infrared Spectroscopy Studies

FT-IR spectrums can determine the interaction between drug and excipient. The FTIR spectra of pure drug (Fig. 16) Manidipine displayed bands at 3026.41 cm^{-1} due to N-H stretch, at 1640 cm^{-1} due to C=O stretching, at 1226.77 cm^{-1}

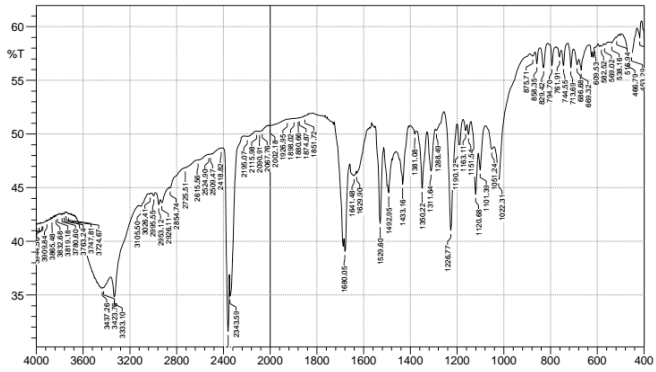

Fig. 16: FTIR spectrum of Manidipine pure drug

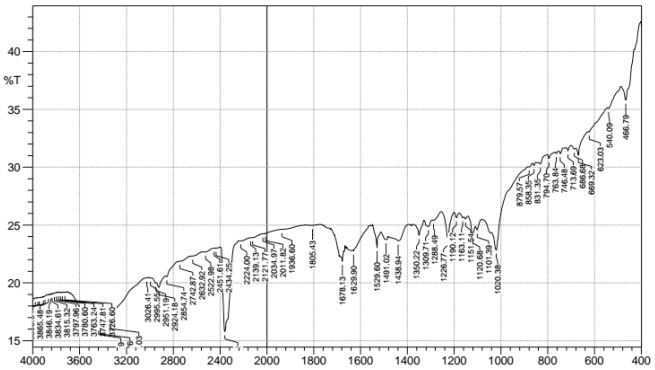

Fig. 17: FTIR spectrum of optimized formulation of Manidipine

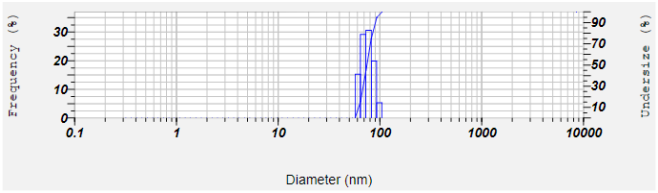

Fig. 18: Particle size analysis of optimized formulation MF11

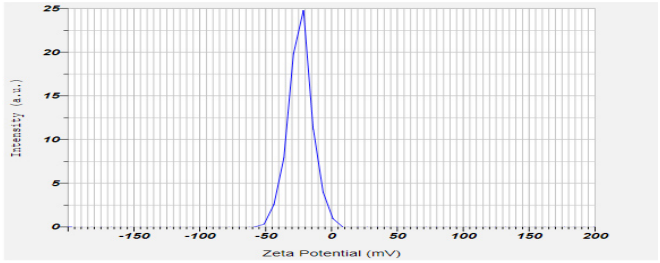

Fig. 19: Zeta potential of the optimized formulation MF11

due to aromatic amine group C-N stretching. The spectra also showed bands at 1288.49 cm^{-1} due to C-N bending. The FTIR spectrum of SNEDDS containing Manidipine (Fig. 17) exhibited characteristic bands consistent with the molecular structure of Manidipine, such as bands at 3095.49 cm^{-1} due to N-H stretch, at 1678.13 cm^{-1} due to C=O stretching, at 1226.77 cm^{-1} due to aromatic amine group C-N stretching. Similar characteristic peaks confirmed a negligible interaction between drug and excipient in Manidipine and Manidipine SNEDDS sample.

Table 5: Parameters after Accelerated Stability Study of optimized formulation MF11

	Temperature Maintained at 40 ± 2^{0}C *Relative Humidity (RH) Maintained at 75% ± 5%RH*			
Parameters	*Initial*	*After 1 month*	*After 2 months*	*After 3 months*
Drug Entrapment Efficiency (%)	98.23 ± 1.74	98.17 ± 1.36	98.11 ± 1.25	98.03 ± 1.88
In Vitro Drug Release (%)	98.79 ± 1.68	98.62 ± 1.23	98.55 ± 1.74	98.27 ± 1.91
#Content uniformity (%)	99.12 ± 1.28	99.07 ± 1.87	98.89 ± 1.62	98.74 ± 1.11

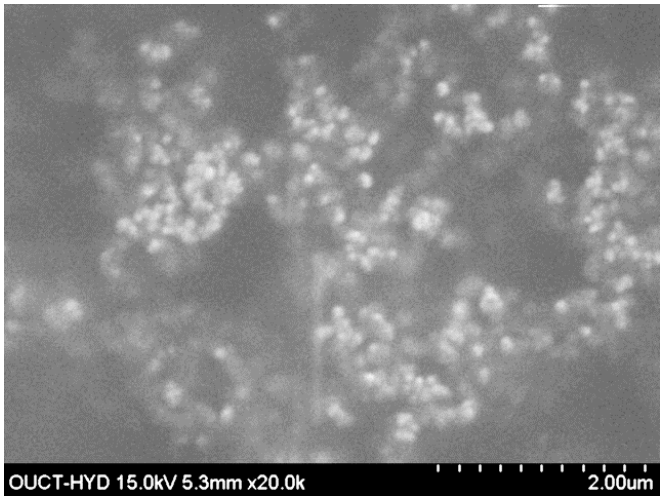

Fig. 20A: SEM images of Manidipine optimized formulations (MF11).

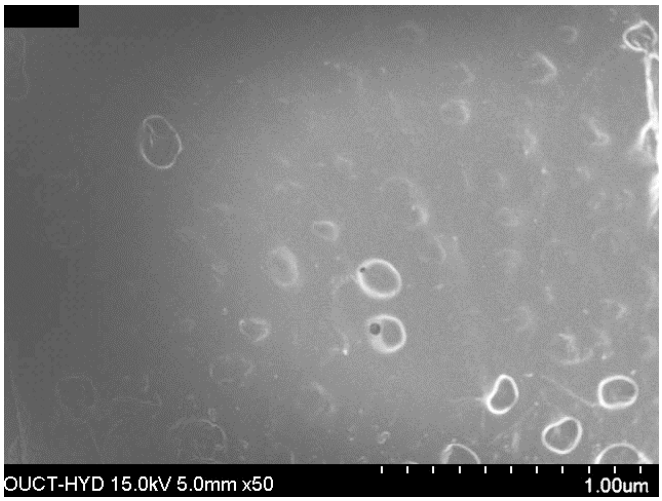

Fig. 20B: SEM images of Manidipine optimized formulations (MF11).

Particle Size Analysis of SNEDDS

The drug absorption is influenced by the rate and extent of drug release, which are dependent on SNEDDS formulation's droplet size. Optimized SNEDDS formulation has (MF11) particle size of 76.5 nm depicting nanometer range of all particles. The mid-range polydispersity was indicated by a Polydispersity index of 0.578 (Fig. 18).

Zeta Potential of SNEDDS

The optimized SNEDDS formulation's zeta potential was -24.7 mV which complied with zeta potential requirement for stability (Fig. 19).

Surface Morphology

Morphological and structural examination of the optimized batches of Manidipine loaded SNEDDS was carried out using transmission electron microscope. SEM images illustrated formation of spherical micelles (Fig. 20a and 20b). These results were in accordance to that of globule size analysis.

Stability Studies

There were no physical changes in appearance and flexibility. After subjecting the optimized formulation (MF11) to the accelerated stability studies, the results were shown that there were no major changes in drug entrapment efficiency, *in vitro* drug release and drug content, hence the formulation was found to be stable (Table 5).

Discussion

An optimized SNEDDS formulation of MF11 consisting of capryol 90 (40.0%), cremophor RH40(10.0%), and triacetin (30.0%) was successfully prepared by applying BBD. The formulations exhibited enhanced drug release in comparison to the pure drug, minimum droplet size (76.5 ± 2.87), best zeta potential (-24.7 ± 1.31mV), and entrapment efficiency (98.23 ± 1.74%) content uniformity (99.12 ± 1.28%) maximum drug release (98.79 ± 1.68%) in 60 minutes. The optimized SNEDDS was analyzed for stability study indicates that the MF11 is stable over 3 months. `Thus, our study confirmed that SNEDDS could be a potential substitute for conventional oral formulations of MF11 for enhanced dissolution rate leading to enhanced drug release and also that development and optimization of SNEDDS for manidipine using a 3-factor, 3-level Box Behnken design was successful in enhancing the release drug release sustainably.

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HOW TO CITE THIS ARTICLE: Jayapal N, Vishnu YV. Development and Evaluation of Manidipine Loaded Self-Nanoemulsifying Drug Delivery System by Box-Behnken Design. Int. J. Pharm. Sci. Drug Res. 2021;13(3):343-352. **DOI:** 10.25004/IJPSDR.2021.130315