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Development and Evaluation of a self-emulsifying drug delivery system (SEDDS) containing Nifedipine

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ABSTRACT

This study aimed to enhance the solubility and bioavailability of Nifedipine through the formulation and optimization of self-emulsifying drug delivery systems (SEDDS). The solubility of Nifedipine in various excipients was investigated, with Capmul MCM, Tween 80, and PEG 400 selected as the oil phase, surfactant, and co-surfactant, respectively, due to their high solubilization capacities. A pseudo ternary phase diagram was constructed to identify the optimal composition for self-emulsification. Formulation optimization using Central Composite Design (CCD) resulted in the identification of an optimized formulation (F4) based on parameters such as globule size, transmittance, emulsification time, and drug release. The prepared S-SEDDS formulation was converted into solid dosage form tablets, with various evaluation parameters assessed to ensure tablet quality. Different methods for Nifedipine extraction were evaluated, and the most efficient method was selected based on recovery percentage. Pharmacokinetic analysis of plasma concentration-time profiles provided insights into drug absorption, distribution, metabolism, and excretion. Finally, the performance of the formulated S-SEDDS tablets was compared with marketed tablets, assessing parameters such as AUC, Cmax, and Tmax to evaluate bioavailability and efficacy. Overall, this study offers valuable insights into optimizing S-SEDDS for Nifedipine delivery, contributing to enhanced solubility and bioavailability.

KEYWORDS Self-emulsifying drug delivery system (SEDDS), Nifedipine.

INTRODUCTION

Nifedipine, a potent calcium channel blocker, is commonly prescribed for the management of hypertension and angina pectoris due to its vasodilatory effects. However, its therapeutic efficacy is often limited by its poor aqueous solubility, which results in erratic absorption and variable bioavailability upon oral administration. Conventional formulations of nifedipine suffer from low and inconsistent plasma drug concentrations, leading to suboptimal clinical outcomes and potential adverse effects. [1, 2]To address these challenges, researchers have focused on developing innovative drug delivery systems capable of enhancing the solubility, dissolution, and bioavailability of poorly water-soluble drugs like nifedipine. One such promising approach is the utilization of self-emulsifying drug delivery systems (SEDDS). SEDDS are composed of oil, surfactant, co-surfactant, and drug, which spontaneously form fine oil-in-water emulsions when exposed to gastrointestinal fluids, thereby improving drug solubilization and absorption. [3, 4]

In recent years, several studies have investigated the formulation and evaluation of SEDDS containing nifedipine to overcome its solubility and bioavailability limitations. These studies have explored various excipients, formulation strategies, and optimization techniques to develop SEDDS formulations with enhanced drug delivery properties. By improving drug dissolution and gastrointestinal absorption, SEDDS have the potential to enhance the therapeutic efficacy and minimize the variability associated with nifedipine therapy.The development of an effective SEDDS formulation for nifedipine involves careful selection of excipients, optimization of formulation parameters, and comprehensive evaluation of physicochemical properties and pharmacokinetic profiles. Excipients such as oils, surfactants, and co-surfactants play critical roles in enhancing drug solubility, emulsification efficiency, and oral absorption. Furthermore, formulation optimization techniques such as central composite design (CCD) and pseudo ternary phase diagrams are employed to achieve desirable drug release kinetics and pharmacokinetic parameters. [5, 6]This research aims to contribute to the advancement of SEDDS technology for improving the oral delivery of Nifedipine by providing a comprehensive overview of the formulation development process, evaluation methodologies, and potential clinical applications. By elucidating the principles underlying SEDDS formulation design and optimization, this study seeks to enhance our understanding of the mechanisms driving enhanced drug solubility and absorption, ultimately leading to improved therapeutic outcomes for patients.

MATERIALS AND METHODS

Materials

Nifedipine was procured from Solanki Enterprises, Pune**.** Other chemicals used during the study were of analytical grade and were used as received from local suppliers.

Methodology

Solubility of Drug

Aqueous solubility determination

The solubility of Nifedipine was determined in distilled water by adding excess quantity of drug to the vial containing distilled water and shaken for 72 hrs. At 40±0.5ºC in an orbital shaker (REMI, Mumbai). After which mixture was centrifuged at 3000 rpm for 15 min, followed by filtration. The filtrates were diluted with methanol and quantified by UV. The measurement was taken in triplicate.

Solubility Study of Nifedipine in Oils, Surfactants and Co-surfactants

The solubility of Nifedipine in various oils (Capmul MCM, Isopropyl myristate, Anise seed oil, Oleic acid, Castor oil and Olive oil), surfactants (Cremophore RH 40, Tween 20, Tween 80 and Span 20) and co-surfactant (PEG400, Transcutol HP and Polyethylene glycol) it was determined.

Procedure-

In a vial, 2 ml of required solvent and excess quantity of the drug was added. The mixture was removed, filtrate and analyze by using UV spectrophotometer. All measurements were done in triplicates.

Preliminary Screening of Surfactants for their Emulsification Ability

Different surfactants were screened for emulsification ability according to the method. Briefly, surfactant to oil in the ratio of 1:1 was mixed (100mg of the surfactants, Cremophore RH 40, Tween 20, Tween 80, and Span 20 were added to 100mg of the oily phase). The mixture of 50 mg was diluted with distilled water and the % transmittance was evaluated 685nm by using UV-spectrophotometer. Emulsions were furthermore observed visually for any turbidity or phase separation.

Preliminary Screening of Co-surfactants

The selected oily phase and surfactant were used for further screening of the co-surfactant for their emulsification ability in the ratio of 3:2:1 of oil, surfactant, and co-surfactant respectively (it gives 1:1 ratio of Oil to S/Comix) Mixtures of 100mg of co-surfactant, 200mg surfactant and 300mg oil were prepared and evaluated similarly as above.

Construction of Pseudo Ternary Phase Diagram

The pseudo ternary phase diagram is a useful and important tool to study the extent of the microemulsion region and phase behavior. The pseudo-ternary phase diagrams were constructed by the water titration method. Add drop wise water to the homogenous liquid mixture of oil, surfactant, and co-surfactant, at ambient temperature (water titration method). The Pseudo ternary phase diagram can be represented in a triangular format (triangle) which has three coordinates. Each coordinate represents one component of the microemulsion system viz.

(1) Oil phase
(2) Surfactant Co-surfactant phase (Smix)
(3) Aqueous phase.

The pseudo ternary phase diagram is constructed to obtain the concentration ranges of components that can result in a large existence area of a microemulsion.

At desired (ratio of surfactant to co-surfactant) value (2:1, 2:2, 2:3) Smix and oil were mixed at ratio of 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1 and 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1 in pre-weighed vial. To the resultant mixtures, water was added drop wise till it forms a clear or slightly bluish appearance, and easily flowable o/w microemulsion. A slightly less clear system, which had a bluish-white or bright white appearance, was defined as an emulsion. No attempt was made to find out other regions except the boundary of the microemulsion region in the ternary phase diagram. After identifying the highest microemulsion region at the desired Smix value, that value was put in Design-Expert software version 8 (Stat-Ease, Inc., Minneapolis, MN, trial version) to prepare liquid SEDDS. The phase diagram was constructed by using Central Composite Design Software (MN, USA, Trial version).

Formulation and optimization using central composite design (CCD)

A two factor central composite design (CCD) was utilized to optimize the composition of Nifedipine SEDDS. CCD is a response surface methodology (RSM). For the present study the CCD methodology was run using Design Expert® software (Version 13.0). The independent

variables of the CCD were amount of oil (X1) and surfactant to co-surfactant and water totaled 100%. Based on the pseudo ternary phase diagram, the range of X1 and X2 were selected. The CCD included factorial points, center point and axial point. The base design consisted of 15 runs. The independent variables and their coded levels and scheme matrix of the CCD are demonstrated in Table below.

Table 1: Factor level and the corresponding values

Independent Variables	Unit	- @	-1	0	+1	+ @
Oil (X1)	%	7.928	10	15	20	22.07
Smix Ratio (X2)	_	0.585	1	2	3	3.414

Table 2: Experimental runs generated through design expert.

Run	X1 Capmul® MCM (%)	X2 (Tween 80: Propylene glycol) (%)	Coded Factors Levels	
			X1	X2
F1	15	3	0	+ @
F2	15	2	0	0
F3	10	1	-1	-1
F4	22	2	+ @	0
F5	10	3	-1	+1
F6	15	2	0	0
F7	20	3	+1	+1
F8	15	2	0	0
F9	15	2	0	0
F10	15	1	0	- @
F11	15	2	0	0
F12	15	2	0	0
F13	15	2	0	0
F14	20	1	+1	-1
F15	8	2	- @	0

% Transmittance (Y1), Globule size (Y2), Self-Emulsification time (Y3) and % Drug Release (Y4) as the response factors were selected (Dependent variables) for assessing the quality of SEDDS, by using Design expert® the responses of all the formulations were treated. The best

fitting model was suggested after comparisons of statistical parameters viz. Standard deviation (SD).

Preparation of Liquid Self-Emulsifying Formulation Loaded with Nifedipine

Accurately weighed Nifedipine and selected excipients Capmul MCM, Tween 80, and Propylene glycol were added to the vial and mixed using a magnetic stirrer for 20 min to aid mixing. Further, the formulations were warmed on a water bath at 40^0C to help in solubilization. The formulations were observed for isotropic and were stored at room temperature until further analysis.

Characterization of Liquid Self-Emulsifying Formulation Loaded with Nifedipine

1. **Thermodynamic stability: [7,8]**

a) **Heating cooling cycle:**

Six cycles between refrigerator temperature 4˚C and 45˚C with storage at each temperature of not less than 48h was studied. Those formulations, which were stable at these temperatures, were subjected to centrifugation test.

b) **Centrifugation:**

Passed formulations were centrifuged at 3500 rpm for 30min. Those formulations that did not show any phase separation were taken for the freeze thaw stress test.

c) **Freeze thaw cycle:**

Three freeze thaw cycles between 4˚C and +25 ˚C with storage at each temperature for not less than 48hr was done for the formulations. Those formulations, which passed these thermodynamic stress tests, were further taken for the dispersibility test for assessing the efficiency of self-emulsification. The formulations were observed visually for any phase separation or color change.

2. **Dispersibility test [8,9]**

The efficiency of self-emulsification of oral L-SEDDS was assessed using a USP dissolution apparatus 2. One millilitre of each formulation was added to 500 ml of water at 37±0.5 ˚C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The *in-vitro* performance of the formulations was visually assessed using the following grading system:

Grade A: Rapidly forming (within 1 min) emulsion, having a clear or bluish appearance.
Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.
Grade C: Fine milky emulsion that formed within 2 min.

3. **Transmittance test [10]**

The stability of L-SEDDS formulation on dilution was checked by measuring transmittance by using a UV-visible spectrophotometer. The transmittance of samples was measured at 685nm for each sample. Three replicate measurements were performed.

4. Determination of self-emulsification time [9,11]

The emulsification time of L-SEDDS was determined by using USP type II dissolution apparatus.

5. Globule size determination [12]

Mean globule size and the polydispersity index of the resulting emulsions were determined by photon correlation spectroscopy (Nanophox, Sympatec, Germany). The sample temperature was set at 25°C and detection was carried out at a scattering angle of 90°.

6. Determination of zeta potential [13]

Zeta potential was measured by photon correlation spectroscopy.

7. *In-vitro* dissolution studies [14]

The quantitative *in vitro* release test was performed in 900 ml of intestinal buffer pH 6.8 containing 2.5% SLS at 50 rpm maintained at 37±0.5°C using the USP type II dissolution apparatus. The samples were withdrawn at different time points. Aliquots of 5 ml samples were withdrawn at regular intervals of time after filtration through 0.45µm pore size membrane filters, and analysis was carried out using UV spectrophotometer at 685nm.

Conversion of L-SEDDS to S-SEDDS of Nifedipine

Formulation of Solid SMEDDS (S-SMEDDS) Solidification of liquid SMEDDS (L- SMEDDS) was performed by using simplest and cheapest adsorption method. For this, the optimized liquid SEDDS formulation (F4) was converted into free-flowing powders by using adsorbents like aerosil 200 and Neusilin US2. The optimized liquid SEDDS was added dropwise to the solid adsorbent and mixed by using mortar and pestle.

Determination of optimal flowable liquid-retention potential (Ø -value) and liquid load factor (Lf) determination for carrier.

1. Powder admixture containing 5 gm of aerosil 200 and Neusilin US2 with increasing quantity were mixed using a mortar and pestle.
2. Each admixture was then placed on a shiny metal plate; the plate was then titled till the admixture slides.
3. The angle formed between the plate and the horizontal surface, at which admixture slides were measured as angle of slide.

Liquid-retention potential (Ø -value)

In constant weight of carrier/coating material, increasing amount of aerosil 200 and Neusilin US2 was incorporated and on each addition, angle of slide was determined. The flowable liquid retention potential (Ø -value) of each liquid/powder admixture was calculated using the following equation.

Ø value = weight of liquid/weight of solid

Determination of liquid load factors

Appropriate amounts of aerosil 200 and Neusilin US2 were used to produce acceptable flowing and compactible powders which were be calculated using following equation.

$$Lf = ØCA + ØCO\ (1/R)$$

Where, Øca and Øco value of aerosil 200 and Neusilin US2.

Preparation of Solid Self-Emulsifying Drug Delivery System (S-SDDS) of Nifedipine:
Adsorption to Solid Carriers:
The optimized liquid SEDDS formulation (F4) was converted into free flowing powders by adsorption onto solid carriers. The solid carriers used for adsorption comprised of materials that provided a high surface area with good disintegration characteristics. The solid carrier used includes Aerosil 200 pharma (B1) and Neusilin US2 (B2). The carrier chosen can absorb at the levels up to 70% (w/w). The conversion process involved addition of liquid formulation onto carriers under continuous mixing in a blender. The powder was dried and was further evaluated for various parameters before comprising it as a tablet formulation. The combination of adsorbent and Liquid SEDDS which showed the best result was used for developing final tablet formulation.

Adsorbent Selection for Optimized Liquid SEDDS Formulation:
The optimized liquid SEDDS formulation was converted into free flowing powder by adsorption of liquid onto solid carriers. The solid carriers used for adsorption materials that provided a high surface area with good disintegration characteristic. The soild carriers used include Aerosil 200 pharma (B1) and Neusilin US2 (B2).The carriers chosen can adsorb up to 75% (w/w).The conversion process involved addition of liquid formulation on solid carriers under continuous mixing. 0.2 ml optimized liquid SEDDS i.e. F4 was used to convert into solid SEDDS. The amount of adsorbents required to achieve a free flowing powder is as shown below in table.

Pre-compression evaluation parameters of powder blend [15]
Before compressing the powder into the tablet form for optimized formulation (F4), powder was subjected to pre compression study. Pre compression parameters confirm the quality of the final dosage form.

1. Bulk density (BD)

Bulk density is defined as the mass of a powder to the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape and the tendency of the particles to adhere to one another.

Procedure-

1. Weigh accurately 25g of granules, which was previously passed through 22#sieve and transferred in 100 ml graduated cylinder.
2. Carefully level the powder without compacting, and read the unsettled apparent volume.
3. Calculate the apparent bulk density in gm/ml by the following formula.

$$\textbf{Bulk density} = \frac{\textbf{weight of powder}}{\textbf{Bulk volume}.}$$

$$\textbf{Db} = \frac{\textbf{M}}{\textbf{V0}}$$

M = mass of the powder; V_0 = bulk volume of the powder.

2. Tapped density (TD): It is the ratio of total mass of powder to the tapped volume of powder
Procedure-

1. Weigh accurately 25 g of granules, which was previously passed through 22# sieve.
2. Transfer granules to 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula.

$$\textbf{Tapped density} = \frac{\textbf{Weigh of powder}}{\textbf{Tapped volume}}$$

$$\textbf{Dt} = \frac{(\boldsymbol{M})}{(\textbf{Vt})}$$

M = mass of the powder; Vt = tapped volume of the powder.

3. Carr's Index:
It is a simple test to evaluate the BD and TD of a powder and the rate at which it was packed down. The formula for Carr's index is as below:

$$\textbf{Compressibility Index}\ (\%) = \frac{\textbf{Density Tapped} - \textbf{Bulk Density}}{\textbf{Density Tapped}}$$

Table 3: Scale of Flowability as per USP.

Compressibility Index (%)	Flow Character
≤10	Excellent
11–15	Good
16–20	Fair
21–25	Passable
26–31	Poor
32–37	Very poor
>38	Very, very poor

4. Hausner's ratio-
Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula,

$$\textbf{Hausner's Ratio} = \frac{\textbf{Tapped Density}}{\textbf{Bulk Density}}$$

Table 4: Relationship between flow character and Hausner ratio as per USP.

Flow Character	Hausner Ratio
Excellent	1.00–1.11
Good	1.12–1.18
Fair	1.19–1.25

Passable	1.26–1.34
Poor	1.35–1.45
Very poor	1.46–1.59
Very, very poor	>1.60

5. Angle of repose [16]

The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

$$\tan\theta = \frac{h}{r}$$

$$\boldsymbol{\theta = tan^{-1}\,(h/r)}$$

Where, θ is the angle of repose, h is the height, r is the radius.

Procedure:

1. The funnel height should be maintained approximately 2–4 cm from the top of the powder pile as it is being formed in order to minimize the impact of falling powder on the tip of the cone.
2. A funnel was filled to the brim and the test sample was allowed to flow smoothly through the orifice under gravity.
3. From the cone formed on a graph sheet was taken to measure the area of pile, there by evaluating the flow ability of the granules. Height of the pile was also measured.
4. Determine the angle of repose by measuring the height of the cone of powder and calculating the angle of repose, a, from the following equation

$$\boldsymbol{\theta = tan^{-1}\,(h/r)}$$

Table 5: Relationship between angle of repose (θ) and flow properties as per USP.

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

Preparation of solid SEDDS

The optimized liquid SEDDS formulation (F4) was converted into free-flowing powders by using adsorbents like aerosil 200 and Neusilin US2. The optimized liquid SEDDS was added drop wise to the solid adsorbent and mixed by using mortar and pestle.

Characterization of S-SEDDS

Powder X-Ray Diffraction (PXRD) analysis [17]

Powder X-ray diffraction (PXRD) study was studied by using an X-ray diffractometer with Cu-Kα radiation (Voltage 40 kV and the current 30 mA). The scanning angle ranged from 5 to 25^0 of 2θ.

Scanning electron microscope analysis [16]

SEM micrograph of the surfaces of the S-SEDDS powder was photographed by using scanning electron microscope.

Formulation and development of solid self-emulsifying drug delivery system (S-SEDDS) tablets [18, 19]

The 3^2 Full factorial design was applied for the tablet S-SEDDS formulation of Nifedipine. The S-SEDDS tablets were prepared by using various super disintegrants like sodium starch glycolate, Crosscarmellose sodium and Crospovidone (PPXL) at different concentrations by direct compression method as shown in Table. Accurately weighed S-SEDDS mixture, Super disintegrants, Povidone, Microcrystalline cellulose, Mannitol and Doshion P-544 DS all material were passed through 40# screen and other ingredients Aspartame and Sodium Stearyl Fumarate were passed through 60 # screen prior to mixing and after this both powder mixture was mixed in blender and collect. Mixed final powder was compressed into tablets by using a rotary tablet machine.

Table 6: Formulation of 3^2 factorial design for S-SEDDS

Composition of Nifedipine S-SEDDS formulations									
Ingredients mg/tab	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
SSEDDS	50	50	50	50	50	50	50	50	50
Crosscarmellose sodium (Ac-Di-Sol)	3	---	---	5	---	---	8	---	---
Sodium Starch Glycolate	---	3	---	---	5	---	---	8	---
Crospovidone (PPXL)	---	---	3	---	---	5	---	---	8
Microcrystalline Cellulose	18	18	18	18	18	18	18	18	18
Mannitol (Pearitol 25C)	90.4	90.4	90.4	85.78	85.78	85.78	82.78	82.78	82.78
Povidone (PVPK-12)	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Doshion P-544 DS	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Aspartame	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Sodium Stearyl Fumarate	3	3	3	3	3	3	3	3	3
Total	**180**	**180**	**180**	**180**	**180**	**180**	**180**	**180**	**180**

All values are in mg.

Evaluation of tablets

Thickness [20]

Thickness of the tablets (n=3) was determined using a Vernier Calliper.

Hardness test [21]

Hardness of the tablet was determined by using the Monsanto hardness tester (n=3) the lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then

forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

Friability test [22]

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting.

Procedure-

1. Initial weight of 20 tablets is taken and these are placed in the Friabilator, rotating at 25 rpm for 4 min.
2. The difference in the weight is noted and expressed as percentage.

It should be preferably between 0.5 to 1.0%.

$$\% \textbf{ Friability} = \frac{(\textbf{W1} - \textbf{W2})}{\textbf{W1}} \times \textbf{100}$$

Where, W1= weight of tablets before test, W2 = weight of tablets after test

Weight Variation test [20]

Procedure -

1. 20 tablets were selected and weighed collectively and individually.
2. From the collective weight, average weight was calculated.
3. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not.

Not more than two of the individual weights deviated from the average weight by more than 5.0% for more than 324 mg tablets.

$$\textbf{Average Weight} = \frac{\textbf{Weight of 20 Tablets}}{\textbf{20}}$$

$$\textbf{Average Variation} = \frac{\textbf{Average Weight} - \textbf{Weight of Each Tablet}}{\textbf{Average Weight}} \times \textbf{100}$$

Drug content [23]

The accurate weight of powder was dissolved in a suitable quantity of intestinal buffer pH 6.8 containing 2.5% SLS at 50 rpm maintained at 37±0.5°C using the USP type II dissolution apparatus. The solution was filtered suitably diluted and the drug content was analyzed using a UV-Visible spectrometer at 276 nm.

***In-vitro* Drug Release Study [24]**

The quantitative *in vitro* release test was performed in 900 ml of intestinal buffer pH 6.8 containing 2.5% SLS at 50 rpm maintained at 37±0.5°C using the USP type II dissolution

apparatus. The samples were withdrawn at different time points. Aliquots of 5 ml samples were withdrawn at regular intervals of time after filtration through 0.45µm pore size membrane filters, and analysis was carried out using UV spectrophotometer at 276 nm.

Bio analytical Method development

In vivo Bio analytical method was developed for formulated Nimodipine SLN (Optimised batch) to determine different pharmacokinetic parameters after ingestion of Nifedipine immediate dissolving Tablet.

Experimental animals

The *in-vivo* study was conducted in accordance with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA, Government of India) guidelines and approved by Institutional Animal Ethics Committee (IAEC), - SGRS College of Pharmacy, and Saswad.

To carry out the study white albino rats weighing 150-200gm were used. The rats were purchased from verified local suppliers and kept in animal house at SGRS College of Pharmacy, Saswad. The temperature of the cage was maintained at 25°C. The rats were divided into 04 groups each containing 04 rats.

Table 7: Animals required

a. Species / Common name	Rat
b. Age / Weight / Size	150 ± 200 gm
c. Gender	Male
d. No. to be used	24
e. Purpose of animal use	*In-vivo* study of self-emulsifying drug delivery system

Reagents and chemicals

S-SEDDS of Nifedipine, Procardia, Acetonitrile, Methanol, buffer (0.1% o-phthaldialdehyde), Na2EDTA solution.

Instruments

Jasco PU-2085 Plus with quaternary gradient pump having UV/VIS detector was used for method development. The HPLC system was built with chromato pro software. HPLC analysis was performed using a Hypersil ODS *C18* (average particle size 5 mm) column (250 mm, 4.6 mm).

Mobile Phase

1. for Nifedipine

The mobile phase consisted of acetonitrile and 0.1% v/v TEA pH (7.4) 80:20(v/v). The eluent was monitored with the UV detector at 326 nm with a flow rate of 1 mL/min and sample size of 20 µL was carried out. For filtration 0.45 mm membrane filter was used.

Preparation of rat plasma sample preparation

1. The liquid-liquid extraction method was used to isolate Nifedipine in rat plasma.
2. Blood samples were collected following oral administration of Nifedipine using S-SEDDS (self-emulsifying drug delivery system) formulations at a dose of 20 mg kg–1 to

overnight fasted (~12 hr.) during fasting animals had free access to water) rats (*n* = 6 each group, 150–200 gm).

3. Blood samples (100µL) were collected into labelled polypropylene tubes containing Na2EDTA solution as an anti-coagulant at pre-dose, 0.15, 0.30, 1, 2, 4, 8, 12, 20 and 24 h from retro-orbital plexus and vortexed for approximately 10 min followed by centrifuging at 4000 rpm at 20°C.
4. Supernatant from each sample was transferred to label through tube and evaporated at 40°C until dryness.
5. These samples were reconstituted with 500 µL of acetonitrile and vortexed briefly and then transferred the sample tube for injection.

Selection of Mobile Phase-

For selecting mobile extraction with different solvents were performed to find suitable mobile phase for Bio analytical method. Extraction was performed with multiple combination for both drugs.

Extraction of Nifedipine with different concentrations.

Preparation of rat plasma sample preparation

1. The liquid-liquid extraction method was used to isolate Nifedipine in rat plasma.
2. Blood samples were collected following oral administration of Nifedipine using S-SEDDS (self-emulsifying drug delivery system) formulations at a dose of 20 mg kg–1 to overnight fasted (~12 hr.) during fasting animals had free access to water) rats (*n* = 6 each group, 150–200 gm).
3. Blood samples (100µL) were collected into labelled polypropylene tubes containing Na2EDTA solution as an anti-coagulant at pre-dose, 0.15, 0.30, 1, 2, 4, 8, 12, 20 and 24 h from retro-orbital plexus and vortexed for approximately 10 min followed by centrifuging at 4000 rpm at 20°C.
4. Supernatant from each sample was transferred to label through tube and evaporated at 40°C until dryness.
5. These samples were reconstituted with 500 µL of acetonitrile and vortexed briefly and then transferred the sample tube for injection.

Preparation of standard stock solution

1. Accurately weigh about 10mg std. tablet and transfer them into 100 mL volumetric flask, add 80 ml of the mobile phase to it.
2. The resulting solution was sonicated for 15 minutes and volume was made up to the mark and filtered through the membrane filter 0.22µ.
3. This filtrate was then used as standard stock solution having concentration 100µg/mL Nifedipine

Preparation of Sample solution

1. Accurately 20 fast dissolving tablets were weighed and triturated in a motor pestle.
4. The tablet powder equivalent to 50mg Nifedipine was accurately weighed and transferred to 100mL volumetric flask.
2. To this 80 mL of mobile phase was added and sonicated for 15 min.
3. The final volume was made up to 100mL with mobile phase and the solution was filtered through the membrane filter 0.22µ.

5. This filtrate was further diluted to yield concentration of 100µg/mL Nifedipine.
4. The total area under Curve (AUC) was calculated verses time by using linear trapezoidal rule.
5. The data was used to calculate $R^2$and regression equation.

MARKETED TABLET

Plasma concentration *vs.* time data of **Nifedipine marketed tablet** was analyzed by Pk solver version 2.0 to derive various pharmacokinetic parameters, *viz.*, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max} and $t½$.

Formulation	Tablet
AUC Calculation Method	Linear Trapezoidal

RESULTS AND DISCUSSION

Solubility determination of Nifedipine

Solubility study

The solubility of a drug in excipients plays an important role in determining the stability of the formulation, as many formulations undergo precipitation before undergoing in situ solubilization. Also to a successful formulation of Nifedipine loaded SEDDS, the entire dose of Nifedipine should be soluble in SEDDS ingredients. The solubility of Nifedipine in various oils, surfactants, and co-surfactants is presented in below table. Among various vehicles screened, Capmul MCM was selected as the oil phase showing the highest solubilization capacity Capmul MCM (15.17±0.08 mg/ml). Tween 80 (12.56±0.04mg/ml) was used as surfactants, and PEG 400 (14.22±0.12mg/ml) was chosen as Co-surfactant.

Table 8: Solubility of Nifedipine (mg/ml) in water

Solvent	Solubility of Nifedipine (mg/ml)	Mean Solubility
Water	5.6	5.5
	5.4	
	5.4	

Table 9: Saturation solubility of Nifedipine in different oil

Sr. No	Oil	Solubility(mg/ml)
1	Oleic acid	12.05±0.04
2	Capmul MCM	15.17±0.08
3	Castor oil	09.58±0.12
4	Aniseed oil	10.23±1.02
5	Isopropyl Myristate	11.42±1.08
6	Olive oil	13.25±1.26

Data are expressed as (Mean ± SD n=3)

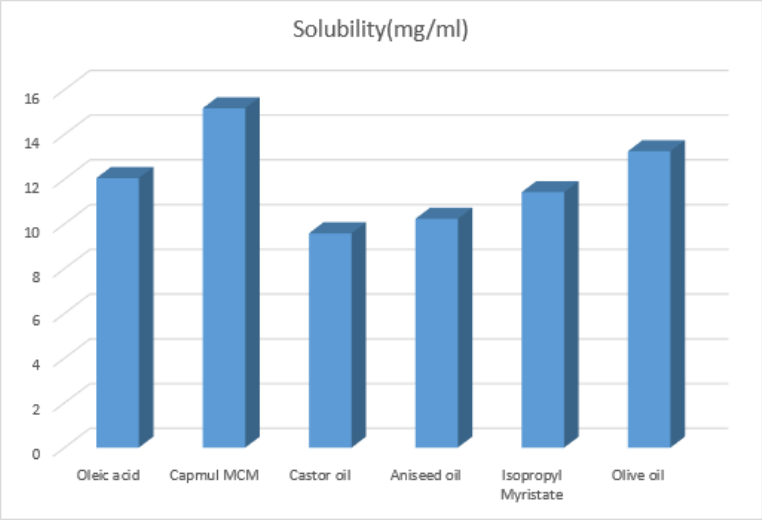


Figure 1: Saturation solubility of Nifedipine in different oils

Preliminary screening of surfactants for their emulsification ability

It has been reported that well-formulated SEDDS is dispersed within seconds under gentle stirring conditions. The results showed that the highest % transmittance, i.e. highest emulsification efficiency, is acquired by Tween 20, followed by Tween 80 > Cremophore RH 40 > Span 20. Tween 80 possessed the highest transmittance value and span 20 the lowest value.

Table 10: Saturation solubility of Nifedipine in surfactant

Sr. No.	Excipients	Solubility (mg/ml)
1	Span 20	10.98± 1.06
2	Cremophore RH40	14.02± 0.89
3	Tween 20	10.25± 1.05
4	Tween 80	15.22±1.34

Data are expressed as mean± SD (n=3)

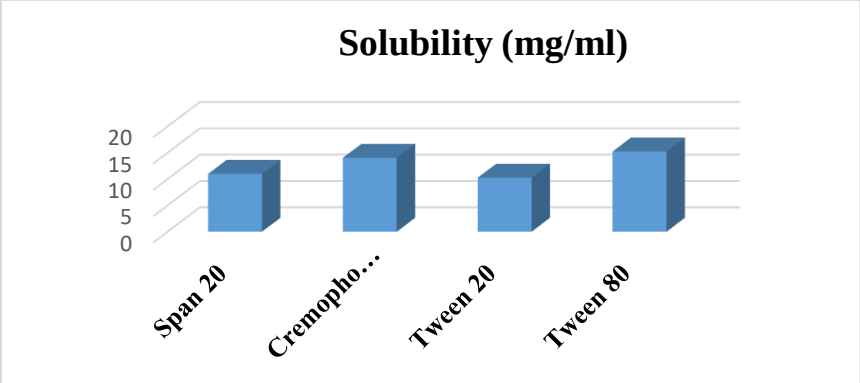


Figure 2: Saturation solubility of Nifedipine in surfactant

Determination of % Transmittance

The percentage of transmittance of the surfactant was checked at 638nm by UV spectrophotometer.

Table 11: Data for Emulsification efficiency of Tween 80 in Oils

Sr. No.	Oils	% Transmittance ± S.D.
1.	Oleic acid	80.124±0.021
2.	Capmul MCM	92.106±0.068
3.	Castor oil	81.740±0.017
4.	Aniseed oil	83.210±0.019
5.	Isopropyl Myristate	86.205±0.010
6.	Olive oil	85.087±0.047

Preliminary screening of co-surfactants

The addition of a co-surfactant to the surfactant-containing formulation was reported to improve dispersibility and drug absorption from the formulation. In the present study, three co-surfactants, namely propylene glycol, polyethylene glycol 400, and Transcutol were compared. Capmul MCM as an oil and Tween 80 as surfactant showed good % transmittance with all the co-surfactant, transmittance 98.12 % with Propylene glycol, > Transcutol 95.24%, > 90.11% with polyethylene glycol 400. In order to formulate SEDDS the components were selected based on Nifedipine and Nimodipine solubility in oily phases and surfactants. Tensile agents and cosurfactants have been screened to verify their capacity to emulsify the oily process. Based on the preliminary screening results, Capmul MCM was selected as an oily step, Tween 80 as a surfactant and Propylene glycol as a co-surfactant.

Table 12: Saturation solubility of Nifedipine in co-surfactant

Sr. No.	Excipients	Solubility (mg/ml)
1	PEG400	16.23± 1.56
2	Transcutol	11.03 ± 1.01
3	Propylene glycol	19.22 ± 1.23

Data are expressed as mean± SD (n=3)

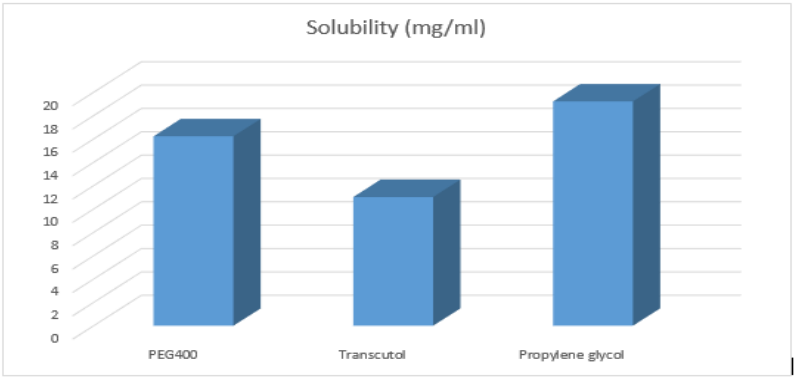


Figure 3: Saturation solubility of Nifedipine in Co-surfactant

Construction of pseudo ternary phase diagram

The pseudo ternary phase diagram of oil (Capmul MCM), surfactant (Tween80), Co-surfactant (Propylene glycol) were constructed with surfactant/co-surfactant ratio of 1:1, 1:2, 1:3. The shaded portion indicates the emulsification region. It was observed that the mixture with 10-20% oil and 80-90% surfactant mixture have shown higher transparency, better stability, and self-emulsification region.

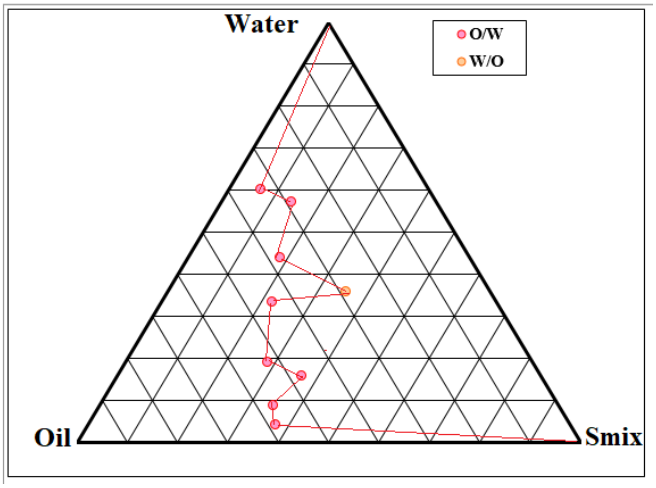


Figure 4: Pseudo ternary phase diagram for different Smix ratio A) 1:1

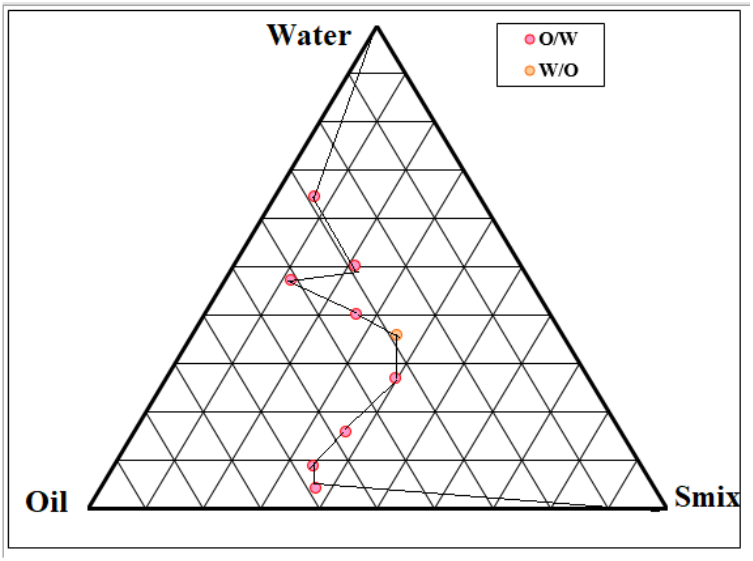


Figure 5: Pseudo ternary phase diagram for different Smix ratio B) 1:2

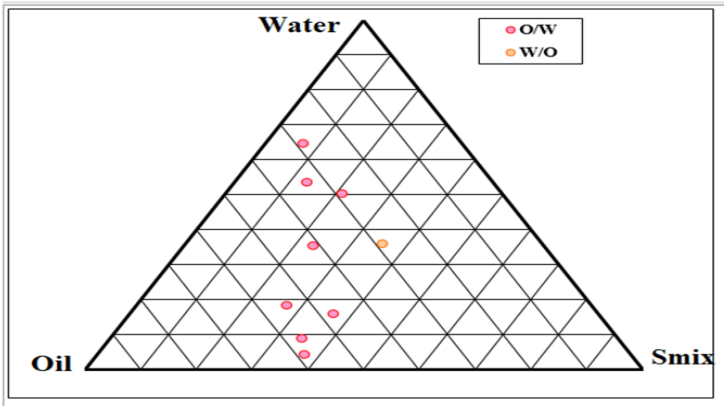


Figure 6: Pseudo ternary phase diagram for different Smix ratio C) 1:3

Formulation and optimization using Central composite design (CCD)

The experimental results of CCD are reported in Table. All the data were computed by Design Expert Software (Version 13.0). The four responses were fitted to Quadratic second –order polynomial model. The model, which shown a lesser P values (≤0.05) and greater F values (Table) was identified as the fitting model. This finding has supported that the formulation factors had significant effect on the responses. The polynomial equation for responses % transmittance, Self-emulsification, Globule size and Drug Release was as follows.

1. Influence of formulation composition factor on Globule size

For assessment of SEDDS, globules size plays critical roles. The smaller globule size provides a larger interfacial area for drug absorption and also permits a faster release rate. The positive coefficient with higher values for X1 in equation shows us that concentration of oils has higher influence on the globule size increases with increasing oil percentage or decrease in ration of surfactant/co-surfactant.

Multiple linear regression analysis of Globule size response revealed that coefficient b1 was found to be positive and b2 and b3 were observed with negative signs. This indicates that increasing amount of oil will decrease the globule size. Similarly, by increasing in the amount of surfactant and cosurfactant, globule size of Nifedipine SEDDS will decrease. A lowest globule size of 56.3 nm was observed for Batch. Increase in globule size could be due to presence of high amount of oil and lesser amount of emulsifier(s) which would lead to poor emulsification of oil. Furthermore, at higher level of surfactant there was a linear decrease in globule size which could be attributed to more amount of surfactant to stabilize the oil-water interface more. Figures depicts the results of response surface graph for globules size analysis.

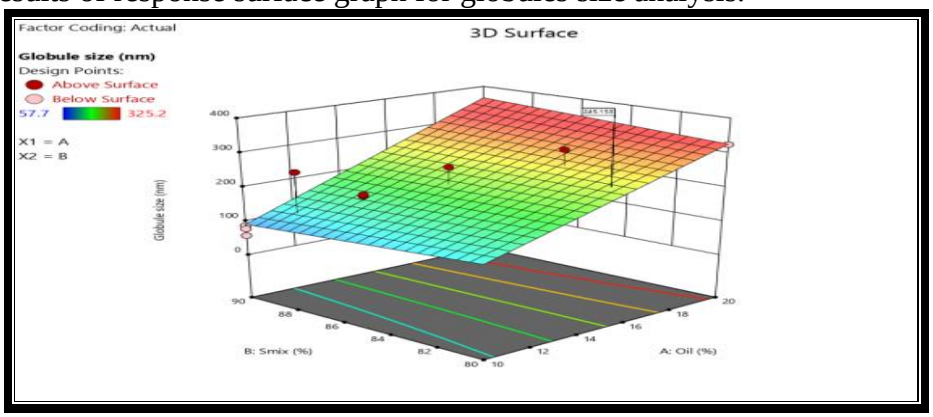


Figure 7: Response surface graph for Globules size analysis

2. Influence of formulation composition factor on % Transmittance

% Transmittance of SEDDS is another important response variable which represent whether the system was monophasic or not on the basis of clarity of system. The negative coefficient with higher value for X1 in equation shows us that concentration of oil has higher influence on transmittance than Smix concentration. The result in response surface graph showed that transmittance increased with decreased in oil concentration.

Multiple linear regression analysis of % transmittance response revealed that coefficient b1 was found to be positive and b2 and b3 were observed with negative signs. This indicates that decreasing amount of oil will increase the % transmittance. Similarly, by decreasing in the amount of surfactant and cosurfactant, % transmittance of Nifedipine SEDDS will increase. A lowest % transmittance of 54.21 and highest % transmittance of 98 was observed for Batch. Figures depicts the results of response surface graph for globules size analysis.

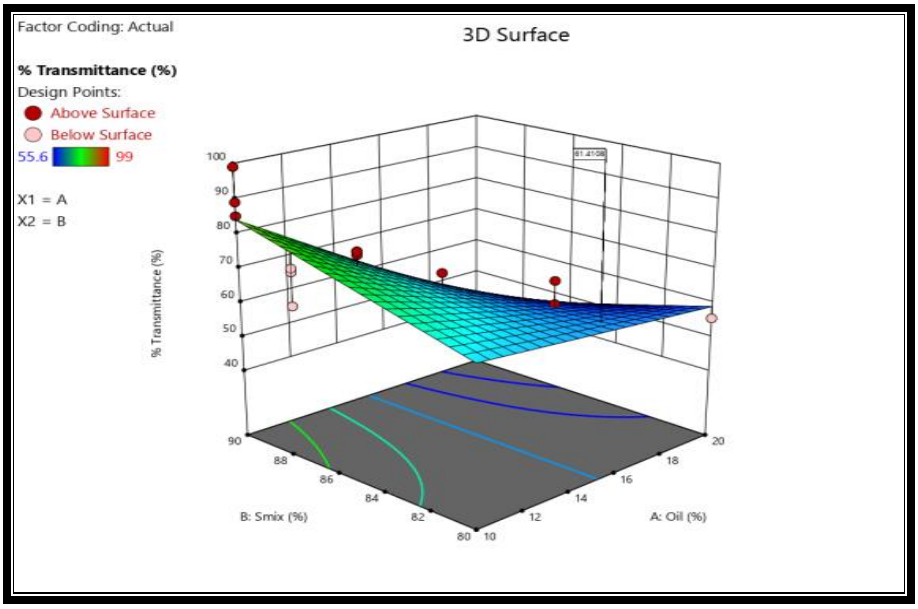


Figure 8: Response surface graph for % transmittance.

3. Influence of formulation composition factor on emulsification

Time required for emulsification generally related to the release characteristics of drug delivery system. Therefore, self-emulsification time of SEDDS was considered as basic response variable which contributed to its assessment. The results in equation and in response surface graph (fig) showed that the increased either with the increase in the percent of the oil or decrease in surfactant: cosurfactant ratio which is correlated to the change in emulsification ability of the system.

Multiple linear regression analysis of Emulsification time response revealed that coefficient b1 was found to be positive and b2 and b3 were observed with negative signs. This shows that decreasing amount of oil will decrease the emulsification time. Similarly, by increasing in the amount of surfactant and cosurfactant, emulsification time of Nifedipine SEDDS will decrease. A lowest emulsification time of 21 sec was observed for Batch. Increase in emulsification time could be due to presence of high amount of oil and lesser amount of emulsifier(s) which would take higher time for emulsification of oil. Furthermore, at higher level of surfactant there was a linear decrease in emulsification time which could be attributed to more amount of surfactant to

stabilize the oil-water interface more. Figures depicts the results of response surface graph for emulsification time.

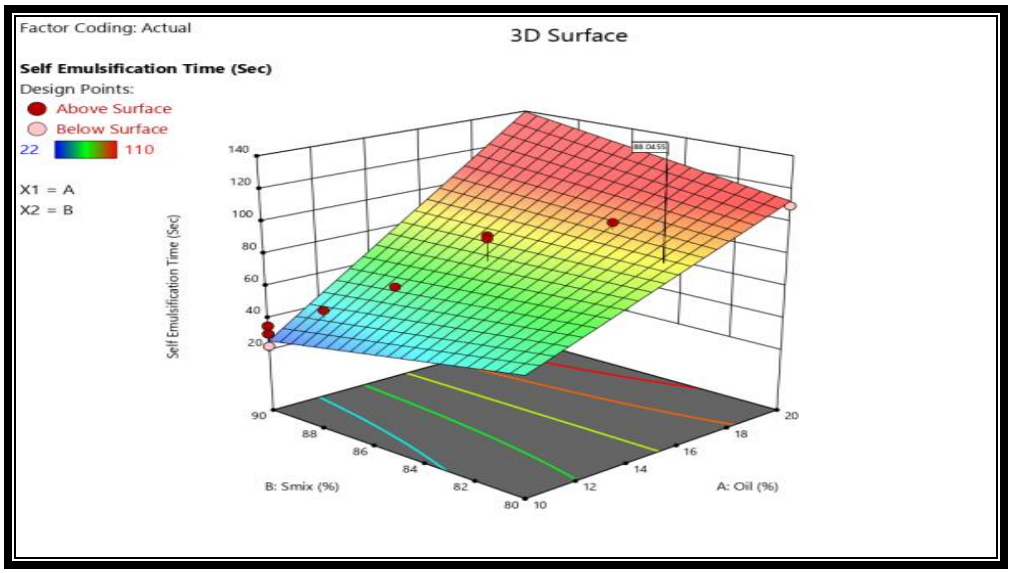


Figure 9: Response surface graph for emulsification time.

4. Influence of formulation composition factor on % drug release

Multiple linear regression analysis of Globule size response revealed that coefficient b1 was found to be positive and b2 and b3 were observed with negative signs. This indicates that increasing amount of oil will decrease the globule size and increase % drug release. Similarly, by increasing in the amount of surfactant and cosurfactant, globule size of Nifedipine SEDDS will decrease and lead to increase in % drug release. A lowest % drug release of 74.25 was observed for Batch. Figures depicts the results of response surface graph for % drug release.

The design reported that the decrease in oil percentage resulted into decrease of globule size, which lead to increases the % drug release.

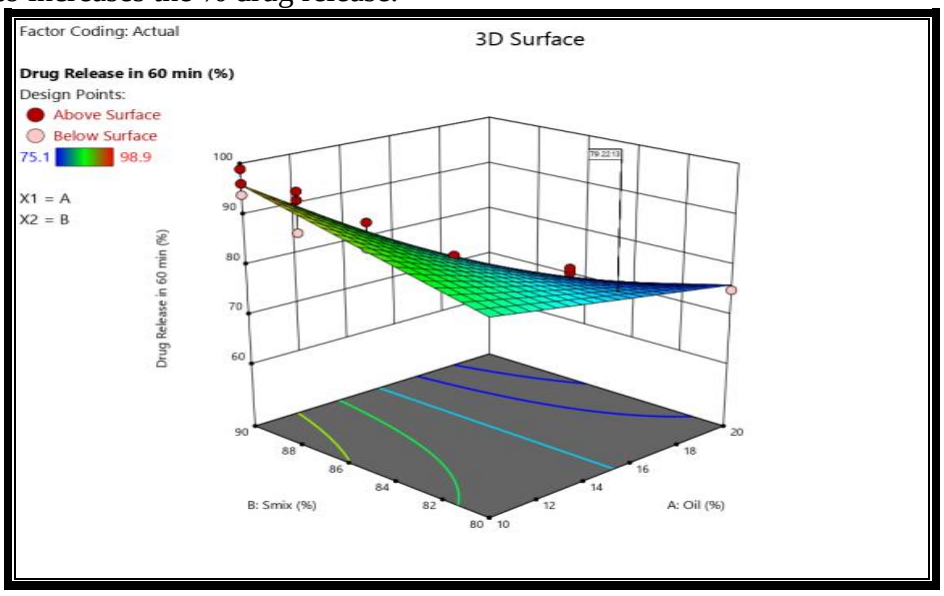


Figure 10: Response surface graph for % drug release.

Table 13: Experimental runs with results of response

Formulations	% Transmittance ± S.D.	Globule size (nm) ± S.D.	Self-emulsification time (Sec.) ± S.D.	Drug Release ± S.D.	PDI ± S.D.	Zeta potential ± S.D.	Drug Content ± S.D.
F1	69.10± 0.20	115.1±1.15	36± 0.63	92.9± 0.35	0.470±1.780	-42.5±0.77	97.41± 0.4
F2	73.981± 0.23	175.2±0.80	50±0.23	85.1± 0.10	0.537±1.210	-30.2±0.22	95.08± 0.15
F3	74.12±0.11	180.2±0.40	60± 0.83	83.4± 0.15	0.545±2.110	-35.2±0.11	94.08± 0.10
F4	98.0± 0.11	56.3±0.36	21± 0.14	98.9± 0.20	0.409±0.460	-69.6±0.34	99.10± 0.10
F5	56.02± 0.34	310.6±2.51	100± 0.94	78.6± 0.10	0.598±2.010	-22.1±0.21	88.51± 0.25
F6	53.21± 0.45	325.2±2.35	110± 0.13	75.1± 0.15	0.610±0.720	-18.8±0.74	88.18± 0.20
F7	62.1± 0.23	260.2±1.82	92± 0.54	80.1± 0.15	0.585±0.170	-35.4±0.27	90.31± 0.1
F8	74.98± 0.55	112.1±0.97	42± 0.51	88.6± 0.30	0.463±0.330	-38.1±0.21	97.01± 0.3
F9	69.15± 0.57	110.1±2.15	45± 0.43	86.5± 0.10	0.458±0.510	-46.1±0.20	96.11± 0.20
F10	88.12± 0.35	78.2±0.85	30± 0.21	96.1± 0.55	0.422±0.220	-89.2±0.21	98.50± 0.50
F11	67.45± 0.42	172.1±1.05	90± 0.45	81.3± 0.10	0.522±0.260	-29.1±0.25	91.10± 0.15
F12	59.12± 0.54	165.8±0.68	60± 0.21	82.1± 0.25	0.515±0.980	-27.4±2.09	94.21± 0.20
F13	57.60± 0.10	245.1±1.19	35± 0.91	94.65± 0.35	0.570±2.100	-40.2±1.28	96.10± 0.20
F14	63.02± 0.42	237.2±1.15	95± 0.88	74.25± 0.25	0.560±0.880	-44.9±1.11	90.68± 0.10
F15	84.33± 0.31	88.2±1.01	35±0.19	93.9± 0.50	0.445±0.190	-85.2±0.71	97.23± 0.15

The design reported that decrease in oil percentage resulted into decrease of Globule size, increase in % Transmittance and decrease in Self emulsification time which lead to increase the % release of the drug which would help to improve solubility. Thus, Formulation (F4) having globule size 56.3nm, % transmittance 98.0%, self-emulsification time 21 sec and % drug release 98.1% in 60 min was found to be optimized. The composition of optimized formulation (F4) of liquid SEDDS of Nifedipine was found to be Capmul CMC 10%. Smix 90%.

Liquid-retention potential (Ø -value)

Liquid retention potential of aerosil 200 and Neusilin US2

Powder admixture containing aerosil 200 and Neusilin US2 were mixed using mortar and pestle and angle of slide was determined. Liquid retention potential of aerosil 200 and Neusilin US2 were shown in Table 14.

Table 14: Result of liquid retention potential (Φ-value) of aerosil 200 and Neusilin US2

Aerosil 200		**Neusilin US2**	
Θ	**Φ value**	**Θ**	**Φ value**
33.02±0.56	**1.6**	**33.15±0.63**	**2.5**
32.05±**0.48**	1.4	**32.52±0.25**	2
32.14±**0.12**	1.2	**31.05±0.14**	2
31.05±**0.23**	1.1	**30.58±0.17**	1.6
32.54±**0.41**	1	**31.59±0.18**	1.4
30.14±**0.48**	0.9	**30.57±0.29**	1.2

The Ø-values was plotted against the corresponding angle of slide (for optimal flow properties). Corresponding to 33^{o} of a liquid/powder admixture represented the flowable liquid-retention potential. The table indicates that the liquid retention capacity of Neusilin US2 is more as compared to Aerosil 200, as the Φ value is more when Neusilin US2 is added as adsorbent for conversion of L-SEDDS to S-SEDDS.

Determination of liquid load factors

The maximum amount of liquid loads on the carrier material, termed ‘‘load factor” (Lf).

Table 15: Result of liquid load factor (aerosil 200)

R	Lf
10:3.2	0.59
10:2.8	0.45
10:2.4	0.39

Table 16: Result of liquid load factor (Neusilin US2)

R	Lf
10:4.4	0.64
10:4	0.48
10:3.6	0.42

From above result, it can be concluded that liquid load factor increase with decreasing adsorbent ratio (R).

From the above result, Neusilin US2 was selected as adsorbent material due to its high liquid retention potential.

Optimization of S-SEDDS:

Two different adsorbents (Aerosil 200 and Neusilin US2) were used to convert liquid SEDDS into free flow powder. Among this Neusilin US2 adsorbent require only 100 mg to convert optimized liquid SEDDS into free flow powder whereas Aerosil 200 requires 120 mg.

Table 17: Adsorbent selection.

Formulation	Adsorbent	Amount of Liquid SEDDS (ml)	Amount of adsorbent required to get free flow powder (mg)
A1	Aerosil 200	0.2	100
A2	Neusilin US2	0.2	80

Table 18: Powder characteristics of adsorbents after adsorption of liquid SEDDS

Adsorbents	Parameters					Inference
	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index %	Hausner's ratio	Angle of repose(°)	
A1	0.518	0.719	25.35	1.28	39.80	Passable
A2	**0.681**	**0.705**	**13.82**	**1.20**	**26.30**	**Excellent**

Evaluation of S-SEDDS tablets of Nifedipine

Tablet evaluation parameters of batch shown in table 16. All parameters were found to be satisfactory and within the specification for the Nifedipine S-SEDDS tablet.

Table 19: Evaluation parameters for S-SEDDS tablets of Nifedipine

Factorial design used 3^3 for preparation of solid SEDDS						
Formulation code	Hardness	Thickness	Uniformity of Weight	Friability	Disintegration time	Drug Content
	(kg/cm2)	(mm)	(mg)	(%)	(sec.)	(%)*
T1	3.90 ± 0.324	2.67 ± 0.084	150.2±1.200	0.08 ± 0.025	42 ± 2.517	98.09 ± 0.811
T2	3.96 ± 0.222	2.73 ± 0.168	149.5±1.300	0.08 ± 0.057	52 ± 2.517	98.21 ± 1.006
T3	4.04 ± 0.198	2.95 ±0.127	149.5±1.200	0.06 ± 0.041	45 ± 3.000	98.15 ± 0.966
T4	**3.78 ± 0.160**	**3.21± 0.119**	**146.23±1.800**	**0.03 ± 0.019**	**27± 2.000**	**98.29 ± 0.270**
T5	4.01 ± 0.222	2.89 ± 0.125	150.5±1.100	0.12 ± 0.116	42 ± 2.517	98.05 ± 0.814
T6	4.00 ± 0.323	2.88 ± 0.168	150.2±1.200	0.06 ± 0.029	72 ± 2.517	98.15 ± 0.654
T7	3.96 ± 0.278	2.81 ± 0.188	149.5±1.500	0.19 ± 0.288	66 ± 4.041	98.22 ± 0.838

T8	4.03 ± 0.324	2.95 ± 0.184	149.8±1.10 0	0.39 ± 0.291	72 ± 2.517	98.11 ± 0.932
T9	3.95 ± 0.232	3.03 ± 0.47	148.8±1.60 0	0.07 ± 0.038	38 ± 2.887	98.08 ± 0.893

Extraction of Nifedipine with different concentrations.

Table 20: % Recovery with different concentrations. (Acetonitrile and 0.1% v/v TEA pH (7.4) 70:30 (v/v)

Methanol	Concentration	AUC	Conc. Found	Recovery (%)
	50	321457	321457.2238	91.8495808
	50	325689	325689.2238	93.0587859
	50	321475	321475.2238	91.854724
	100	601478	601478.2	90.20582
	100	610258	610258.2	91.52259
	100	603258	603258.2	90.47278
	150	901475	901475.2	96.70974
	150	905214	905214.2	97.11086
	150	901485	901485.2	96.71081

Table 21: % Recovery with different concentrations. (Acetonitrile and 0.1% v/v TEA pH (7.4) 80:20 (v/v)

acetonitrile: 0.1% o-phthaldialdehyde	Concentration	AUC	Conc. Found	Recovery (%)
	50	341457	341457.2238	97.5641604
	50	341569	341569.2238	97.5961621
	50	345625	345625.2238	98.7550788
	100	645784	645784.2	96.85055
	100	641557	641557.2	96.21662
	100	641458	641458.2	96.20177
	150	924587	924587.2	99.18918
	150	924718	924718.2	99.20324
	150	923569	923569.2	99.07997

Table 22: % Recovery with different concentrations. (Acetonitrile and 0.1% v/v TEA pH (7.4) 90:10 (v/v)

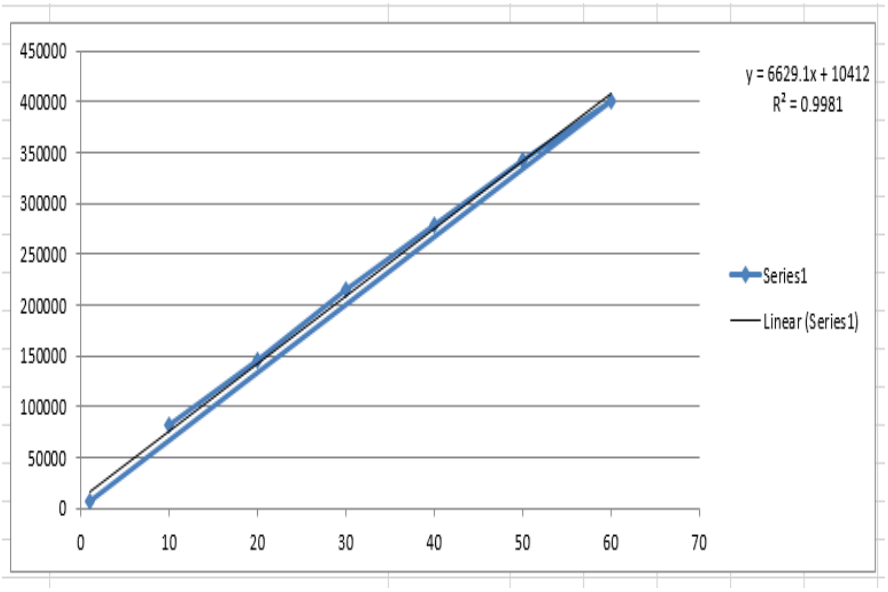
Acetonitrile	Concentration	AUC	Conc. Found	Recovery (%)
	50	321478	321478.2238	91.8555811
	50	321455	321455.2238	91.8490094
	50	312478	312478.2238	89.2840203
	100	612478	612478.2	91.85553
	100	612581	612581.2	91.87098
	100	624784	624784.2	93.70111
	150	895547	895547.2	96.07379

	150	897485	897485.2	96.28169
	150	895669	895669.2	96.08687

Hence, acetonitrile and 0.1% v/v TEA pH (7.4) 80:20 (v/v) showed maximum extraction at a concentration range 50.0–150.0 ng/mL; thus used as mobile phase.

Linearity

Linearity of the method was evaluated by preparing a standard solution containing 100 µL of Nimodipine. Sequential dilutions were performed to give solutions at 10-60µg/ml. These were injected and peak areas used to plot calibration curves against the concentration. The correlation coefficient values of these three analytes were 0.999. The results are shown in Table 5.



Graph 1. Linearity graph.

PK data analysis

Plasma concentration *vs.* time data of Nifedipine was analyzed by Pk solver version 2.0 to derive various pharmacokinetic parameters, *viz.*, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max} and $t½$.

Formulation	Optimised Batch
AUC Calculation Method	Linear Trapezoidal

Table 23: Summary Table- Input Variable

Time In Hr.	**Time in Minutes**	**Plasma Drug Conc. Mcg/ml**
0	**0**	**0**
0.15	15	5.45
0.5	30	8.9
1	60	13.56
2	120	15.23

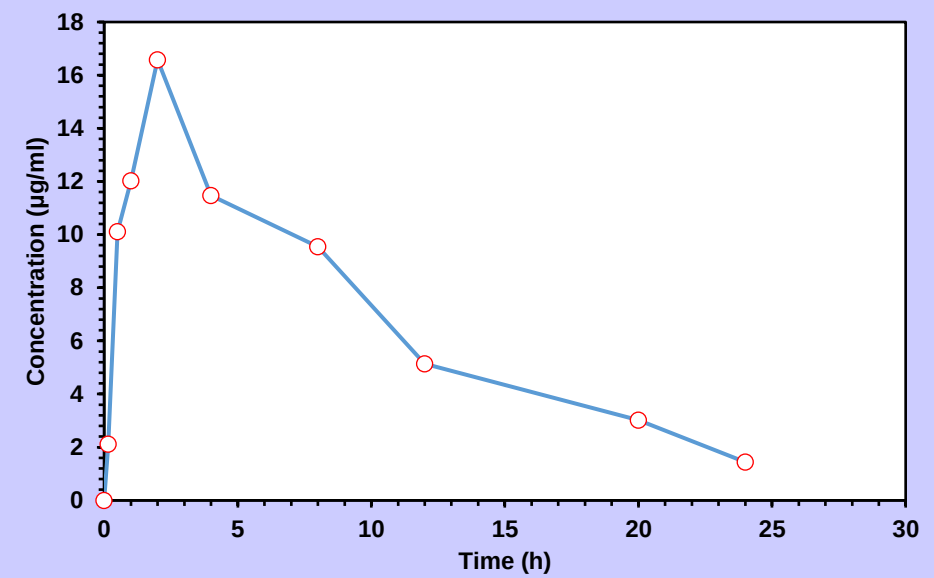
4	240	10.23
8	480	7.24
12	720	6.32
20	1200	2.98
24	1440	2.11

Table 24: Summary Table- Output

Time	Conc	ln(C)	AUC	AUMC	R	R adj
0	0		0	0		
0.15	2.12	0.75141609	0.159	0.02385		
0.5	10.11	2.31352503	2.29925	0.964125		
1	12.02	2.48657193	7.83175	5.232875		
2	16.58	2.80819715	22.13175	27.822875	-0.9888044	0.97216761
4	11.47	2.43973493	50.18175	106.862875	-0.9843448	0.95857963
8	9.55	2.25654115	92.22175	351.422875	-0.9811432	0.94396304
12	5.14	1.63705308	121.60175	627.582875	-0.9597758	0.84233935
20	3.02	1.10525683	154.24175	1115.90288		
24	1.44	0.36464311	163.16175	1305.82288		

Table 25: Calculation Results

Parameter	Unit	Value
Lambdaz	1/h	0.102937439
t1/2	h	6.733674217
Tmax	h	2
Cmax	µg/ml	16.58
Tlag	h	0
Clast_obs/Cmax		0.086851628
AUC 0-t	µg/ml*h	163.16175
AUC 0-inf_obs	µg/ml*h	177.1508293
AUC 0-t/0-inf_obs		0.921032945
AUMC 0-inf_obs	µg/ml*h^2	1777.459625
MRT 0-inf_obs	h	10.03359472
Vz/F_obs	(mg)/(µg/ml)	1.096764654
Cl/F_obs	(mg)/(µg/ml)/h	0.112898145



Graph 2. Time in (min) Vs Concentration (µg/ml)

2. MARKETED TABLET

Formulation	Tablet
AUC Calculation Method	Linear Trapezoidal

Table 26: Summary Table- Input Variable

Time In Hr	Time in Minutes	Plasma Drug Conc. Mcg/ml
0	**0**	**0**
0.15	15	4.12
0.5	30	7.9
1	60	12.51
2	120	14.69
4	240	9.26
8	480	6.23
12	720	6.11
20	1200	1.56
24	1440	1.89

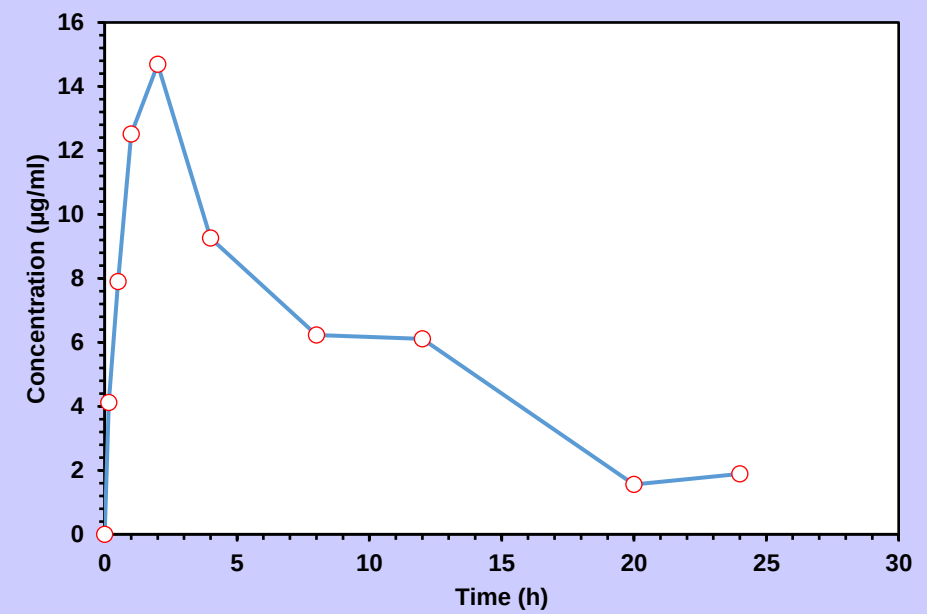
Table 27: Summary Table- Output

Time	Conc	ln(C)	AUC	AUMC	R	R adj
0	0		0	0		
0.15	4.12	1.41585316	0.309	0.04635		

0.5	7.9	2.06686276	2.4125	0.84575		
1	12.51	2.52652832	7.515	4.96075		
2	14.69	2.68716699	21.115	25.90575	-0.963038	0.90930267
4	9.26	2.22570405	45.065	92.32575	-0.9491706	0.86789969
8	6.23	1.82937633	76.045	266.08575	-0.9221383	0.77550863
12	6.11	1.80992677	100.725	512.40575	-0.8944227	0.59998388
20	1.56	0.44468582	131.405	930.48575		
24	1.89	0.63657683	138.305	1083.60575		

Table 28: Calculation Results

Parameter	Unit	Value
Lambda_z	1/h	0.097041102
t1/2	h	7.142820581
Tmax	h	2
Cmax	µg/ml	14.69
Tlag	h	0
Clast_obs/Cmax		0.128658952
AUC 0-t	µg/ml*h	138.305
AUC 0-inf_obs	µg/ml*h	157.7812834
AUC 0-t/0-inf_obs		0.87656151
AUMC 0-inf_obs	µg/ml*h^2	1751.737933
MRT 0-inf_obs	h	11.10231769
Vz/F_obs	(mg)/(µg/ml)	1.306227407
Cl/F_obs	(mg)/(µg/ml)/h	0.126757747



Graph 2. Time in (min) Vs Concentration (µg/ml)

CONCLUSION

The novel SEDDS formulation for Nifedipine, utilizing Capmul MCM, Tween 80, and propylene glycol, successfully enhanced the drug's solubility, self-emulsification efficiency, and release profile. The transition to S-SEDDS using Neusilin US2 yielded a solid dosage form with excellent flow properties, indicating its potential for commercial production and improved therapeutic efficacy.

CONFLICT OF INTEREST

None declared by authors.

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