Research Article

Innovative Self-Emulsifying Drug Delivery System for Enhanced Nevirapine Bioavailability: Formulation and Evaluation

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Received: 09-05-2025; **Revised:** 25-07-2025; **Accepted:** 08-08-2025; **Published online:** 20-08-2025.

ABSTRACT

This study presents the development and optimization of a self-emulsifying drug delivery system (SEDDS) for Nevirapine (NVP), a BCS Class II non-nucleoside reverse transcriptase inhibitor (NNRTI) used in HIV therapy. Our goal was to significantly enhance NVP's oral bioavailability through a comprehensive in vitro dissolution study. We systematically evaluated NVP's solubility across various vehicles to identify the most effective component combinations. Utilizing Chromophore RH40 as the surfactant, PEG400 as the co-surfactant, and Carbomer 940 as the oil phase, we constructed detailed pseudo-ternary phase diagrams. From this analysis, we selected eight formulations featuring Carbomer 940 with Smix ratios of 1:1, 2:1, and 3:1. The findings demonstrate that the NVP-loaded SEDDS exhibit superior solubilization and nanosizing capabilities, effectively enhancing drug absorption and paving the way for improved therapeutic outcomes.

Keywords: Nevirapine, Self-emulsifying drug delivery system (SEDDS), BCS Class II drugs, Nanosizing, solubility enhancement.

INTRODUCTION

A non-nucleotide reverse transcriptase inhibitor called nevirapine (NVP) is used to treat HIV infection. NVP is a medication classified as BCS class II medicine, meaning it has high permeability and poor solubility. The oral route is the most traditional and practical way to provide therapeutic drugs since it is easy to administer and results in lower therapy costs and greater patient compliance[1-4]. The low water solubility of around 40% of novel chemical entities poses a significant challenge to the current medication delivery technology. The solubilization of these medications in the gastrointestinal (GI) tract frequently serves as the rate-limiting step for their absorption. These medications, which have high permeability and poor water solubility, are categorized by BCS as class II medicines. Because they can hold the medication in the dissolved state until it is absorbed, lipid-based drug delivery systems have been shown to be helpful in boosting the bioavailability of highly lipophilic substances[5,6]. This helps them get over the obstacle of sluggish dissolving rates. Lipid formulations can be as simple as pure oils or as complex as formulations with varying amounts of co-solvents, surfactants, or surfactants. In order to increase the oral bioavailability of poorly water-soluble medications, a number of research recently concentrated on micro emulsion formulations, with a focus on self-emulsifying or self-emulsifying drug delivery systems (SEDDS)[7,8]. Therefore, in order to improve the bioavailability of weakly water-soluble medicines and achieve more effective therapeutic effects, alternate oral routes of delivery must be developed. One of the more intriguing methods for enhancing the oral absorption, dissolution, and solubility of weakly water-soluble medications is the use of SEDDS. This research project is mainly focused on the development of an NVP loaded SEDDS suitable for the oral administration to the HIV patients [9,10].

RESOURCES AND TECHNIQUES

Materials NVP were bought from a nearby vendor. PEG 400, Cremophore RH40, and Carbomer 940 were acquired from Solanki Enterprises in Pune. The other substances were all analytically graded.

Approaches Solubility analysis [11,12]

It was determined whether NVP was soluble in a variety of oils, surfactants, and co-surfactants, such as Olieic acid, Arachis oil, Captex 300, Castor oil, Soybean oil, Isopropyl myristate, Labrafil, Olive oil, and Almond oil. A vial was filled with an excess of drug and two millilitres of the required solvent. The equilibrated mixture was taken out, filtered, and then subjected to analysis using a UV-visible spectrophotometer (JASCO V-630). Three measurements of each were made.

Preliminary screening of surfactants

A By adding 100 mg of each surfactant, Cremophore RH 40, Tweens 80, and Span 20 to 100 mg of the oily phase, a 1:1 combination of surfactant and oil was created. Next, using a UV spectrophotometer (JASCO V-630), the mixture's percentage transmittance was determined at 638.2 nm. These emulsions were also visually inspected for turbidity and phase separation.

Preliminary screening of co-surfactants

The selected oily phase and surfactants were used in a ratio of 3:2:1 for oil, surfactant, and co-surfactant, respectively, resulting in a 1:1 ratio of oil to S/Comix. This was done in order to further test the various co-surfactants for their ability to emulsify. As was previously indicated, mixtures

comprising 200 mg of surfactant, 100 mg of co-surfactant, and 300 mg of oil were prepared and evaluated.

Pseudo-ternary phase diagram construction [13]

Using the water titration approach, the pseudo-ternary phase diagrams were generated. For any composition, the surfactant, co-surfactant, and oil concentrations should always be administered in total to 100%. Smix and oil were combined in a pre-weighed vial at the necessary (ratio of surfactant to co-surfactant) value (1:1, 2:1, 3:1, and 1:2) at ratios of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1. The resultant mixtures were mixed with water dropwise until easily flowable o/w microemulsions formed, either clear or slightly bluish in hue. The somewhat less translucent system that appeared brilliant white or bluish white was categorized as an emulsion. To manufacture liquid SEDDS, the highest microemulsion region at the appropriate Smix value was found, and that value was entered into the Design-Expert software version 8. The Central Composite Design software (MN, USA, Trial edition) was used to create the phase diagram.

Preparation of liquid self-emulsifying formulation loaded with Nevirapine by using central composite design

Nevirapine that had been weighed accurately and the selected excipients (PEG 400, Cremophor RH 40, and Carbomer 940) were added to the vial and mixed with a magnetic stirrer for fifteen minutes. The formulations were further heated to 400 degrees Celsius in a water bath to facilitate solubilization. The formulations were stored at room temperature until further analysis once their isotropicity was verified.

Characterization of formulations

1. Analysis using X-ray diffraction (XRD) [14,15]

X-ray diffractometer with Cu-Kα radiation (voltage 40 kV, current 30 mA) was used to study X-ray diffraction (XRD) research. The range of the scanning angle was 5 to 250 of 2θ.

2. The test of transmittance [16-17]

A UV-visible spectrophotometer was used to measure the transmittance in order to verify the stability of the SEDDS formulation on dilution. At 638.2 nm, the transmittance of every sample was measured.

3. Calculating the time required for self-emulsification [16-17]

Using the USP dissolving test apparatus II, 1 milliliter of each formulation was added to 900 milliliters of distilled water and continuously stirred at 50 revolutions per minute at 37 ± 0.5ºC. The emulsification time was measured in seconds and was judged to be the amount of time needed to disseminate the system evenly and completely.

4. Measurement of cloud points [18]

Every formulation was put in a water bath that was gradually heated and diluted with distilled water in a ratio of 1:250. A cloud point is the location where clouds begin to form.

5. Determination of globule size [19]

The resulting emulsions' mean globule size and Polydispersity index were calculated using photon correlation spectroscopy (Nanophox, Sympatec, Germany). A scattering angle of 90° was used for detection, and the sample temperature was maintained at 25°C.

6. Zeta potential calculation [19]

The photon correlation spectroscopy method was used to detect the zeta potential.

7. Determination of drug content [20]

Self-emulsifying formulations were dissolved in methanol. Then solution was filtered and determined the absorbance on UV-Visible spectrophotometer by using diluted self-emulsifying formulation without drug as a blank at 263 nm.

8. Dissolution experiments conducted in vitro [21]

An in-vitro release test was conducted using a USP type-II dissolving test apparatus in 900 mL of 0.1N HCl kept at 37 ± 0.5°C. Every two, five, ten, fifteen, twenty, thirty, forty, and sixty minutes, 5 ml aliquots were taken and replaced with new dissolving medium. Following filtration via a membrane filter with a pore size of 0.45 µm, analysis was performed at 283 nm using a UV-Visible spectrophotometer.

9. Analysis of stability [21,22]

The ICH criteria were followed in evaluating the stability test. Evaluations of SEDDS's appearance, self-emulsifying qualities, transmittance, drug content, and drug release percentages were conducted.

RESULTS AND DISCUSSION

The self-emulsifying drug delivery system, or SEDDS, is a great way to distribute medications that fall into classes II and IV of the Bio pharmaceutics Classification System (BCS) since it can help improve the in-vitro performance of poorly water-soluble medicines.

Study of Solubility

Since many formulations precipitate prior to in situ solubilisation, a drug's solubility in excipients is a significant factor in determining the formulation's stability. Additionally, all of the NVP dosage needs to dissolve in the SEDDS components for the formulation of NVP loaded SEDDS to be successful. Tables Nos. 1 and 2 show the solubility of NVP in different oils, surfactants, and co-surfactants. Carbomer 940 was chosen as the oil phase with the highest solubilisation capability (62.12 ±1.02 mg/ml) among the different vehicles examined. PEG 400 (54.36 ± 1.01 mg/ml) was selected as the co-surfactant and chemophore RH40 (78.29± 0.55 mg/ml) was utilised as the surfactant.

Table 1: Solubility of NVP in various oils

Sr. No.	Oils	Solubility (mg/ml)
1	Carbomer 940	62.12 ± 1.02
2	Capryol 90	44.12 ± 0.58
3	Oleic acid	36.98 ± 0.11
4	Arachis oil	41.02 ± 0.98
5	Captex 300	39.54 ± 0.77
6	Castor oil	37.44 ± 0.47
7	Soyabean oil	21.15 ± 0.56

Data expressed as mean ± SD (n = 3)

Table 2: Solubility of NVP in various surfactants & co-surfactants

Sr. No.	Surfactants & Co-surfactants	Solubility (mg/ml)
1	Cremophore RH40	78.29 ± 0.55
2	Tween 80	72.11 ± 0.15
3	Tween 20	60.15 ± 0.26
4	Span 20	54.11 ± 0.87
5	PEG 400	74.36 ± 1.01
6	Transcutol	49.88 ± 0.18
7	Propylene glycol	41.12 ± 0.66

Data expressed as mean ± SD (n = 3)

Table 3: Emulsification ability of selected surfactants and co-surfactants by using Carbomer 940 as an oily phase

Sr. No.	Surfactants & Co-surfactants	%Transmittance
1	Cremophore RH40	97.12 ± 0.89
2	Tween 80	91.17 ± 0.58
3	Tween 20	8.29 ± 0.87
4	Span 20	49.78 ±0.58
5	PEG 400	98.47 ± 0.17
6	Transcutol	95.89 ± 0.85
7	Propylene glycol	91.14 ± 0.65

Data expressed as mean ± SD (n = 3)

Preliminary assessment of surfactants' capacity for emulsification

A well-formulated SEDDS has been shown to dissolve in a matter of seconds when gently stirred. The sequence listed in Table No. 3 of the results is what is utilised to have the highest emulsification efficiency, or maximum percentage transmittance: Cremophore hierarchy: RH 40 > Tween 80 > Tween 20 > Span 20. The Cremophore RH 40 had the maximum transmittance rating, whereas Span 20 had the lowest.

Preliminary co-surfactant screening

This study compared three co-surfactants: propylene glycol, transcutol, and PEG 400. When Carbomer 940 was utilised as an oil and Cremophor RH40 was used as a surfactant, transmittance with all of the cosurfactants was good. PEG 400 had a transmittance of 97.12%, while propylene glycol had a transmittance of 95.89% > 98.47%. Based on the results of the preliminary screening, Carbomer 940 was selected as the oily phase, Cremophor RH40 as the surfactant, and PEG 400 as the cosurfactant.

Construction of pseudo-ternary phase diagram

A simple pseudo-ternary phase diagram comprises three components: water, oil, and Smix. Each phase diagram corner represents 100% of each component. Campul MCM was used as the oil phase, Cremophore RH40 as the surfactant, and PEG400 as the co-surfactant to produce unique phase diagrams. The information obtained from the solubility research and the initial screening of surfactants and cosurfactants were used to make these decisions.

The pseudo-ternary phase diagram composed of (Carbomer 940 + Cremophor RH40 + PEG 400) in different surfactant/co-surfactant ratios of 1:1, 1:2, 2:1, and 3:1 was constructed using the water titration method. The shaded area represents a micro/nano emulsion region, while the larger region indicates a better ability for self-nano emulsification.

Table 4: Characterization parameters of NVP-SEDDS formulations

Formulations	% Transmittance ± S.D.	Self-emulsification time (Sec.) ± S.D.	Globule size (nm) ± S.D.	Drug Content (%) ± S.D.	Cloud Point (°C) ± S.D.
F1	97.44 ±0.45	27.02 ± 0.25	15.48 ± 0.71	95.23 ± 0.95	63.8± 0.58
F2	97.48 ± 0.89	22.14 ± 0.47	21.02 ± 0.25	94.58 ± 0.78	65.4±0.96
F3	96.59 ± 0.25	25.14 ± 1.58	22.58 ± 1.08	98.12 ± 0.52	70.1±0.78
F4	98.44 ± 0.27	34.12 ± 1.00	17.02 ± 0.59	97.44 ± 0.26	69.5 ± 0.57
F5	98.88± 0.96	21.30 ± 0.47	18.78 ± 0.77	98.78 ± 0.25	69.8 ± 0.51
F6	96.02± 0.22	31.02 ± 0.89	22.09 ± 1.07	95.58 ± 0.78	65.8 ± 0.89
F7	97.10 ± 0.18	28.77 ± 0.77	19.65 ± 0.89	97.49 ± 0.55	74.2 ± 0.78
F8	95.55 ± 0.55	42.66 ± 0.25	21.17 ± 0.45	96.59 ± 0.69	68.5 ± 1.25

Data expressed as mean ± SD (n = 3)

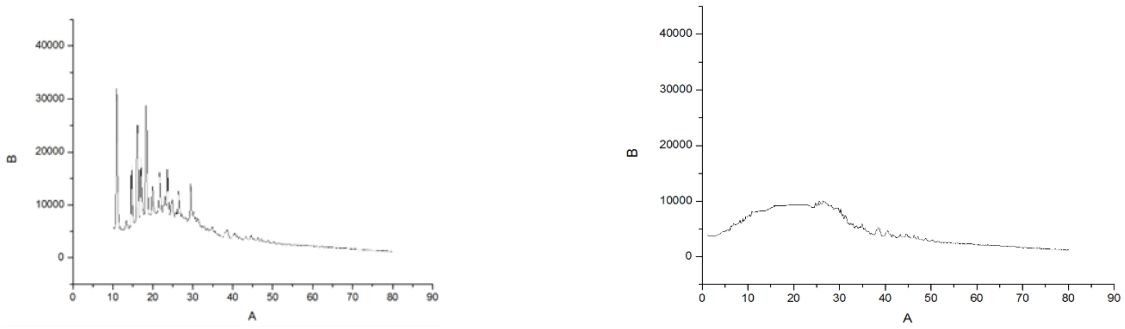

Figure 1: (a) XRD spectra of pure drug (b) XRD spectra of optimized formulation (F5)

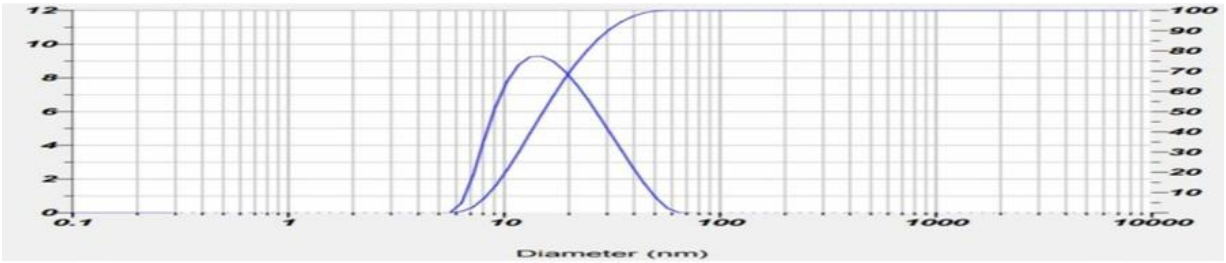

Figure 2: Globule size distribution of F5 formulation

X-ray diffraction (XRD) analysis

XRD studies of Nevirapine pure drug showed several sharp peak. The SEDDS prepared for Nevirapine optimized formulation (F5) revealed that sharp peak of mixture was observed at 15-25^{0}θ. The XRD patterns are shown in figure 1 a & b.

Determination of self-emulsification time

The table displayed the self-emulsification time results. Formulation F5 showed the lowest self-emulsification time of 16.55 seconds.

Cloud point measurement

The cloud point of all the SEDDS formulations were above 61.2°C as shown in table.

Globule size determination:

The average globule size of F5 formulation was found to be 12.03 nm which was found to be minimum amongst all other formulation as shown in figure. The polydispersity index of F5 formulation was found to be 0.144.

Zeta potential determination

The zeta potential of all SEDDS formulations with values ranging from −26.25. to −51.11 mV, indicating a stable system and well-separated emulsion globules.

Drug content

The content of the drug in selected SEDDS formulations was reported in the range of 92.15-96.55%.

***In-vitro* dissolution studies**

USP type-II dissolving apparatus was used for in-vitro dissolution tests in 0.1 N HCl in order to compare the drug release from various SEDDS formulations (F1-F8). A dissolving study was conducted on the SEDDS formulation, and the results are shown in Figures. After 30 minutes, the F5 optimised formulation demonstrated a maximum drug release of 96.55%. Therefore, it can be said that the NVP's solubilization and release rate were enhanced by the formulation of SEDDS.

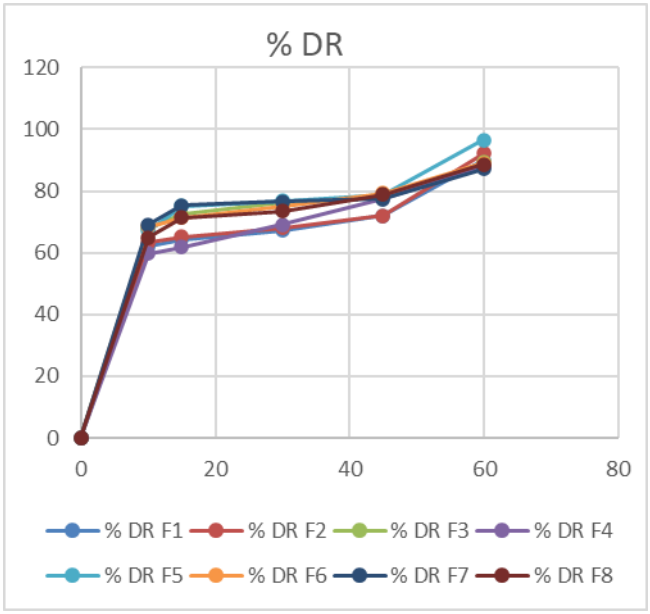

Figure 3: *In-vitro* drug release profile of formulations F1 to F8

Stability study of F5 liquid SEDDS formulation

The effect of stability condition on storage for 6 months on F5 formulation was studied. The percent transmittance, drug content and drug release were not reduced considerably. From a stability study, it can be concluded that the F5 formulation retained its stability and it was found to be stable during the sixth-month stability study.

Table 5: Stability study data of F5 formulation of liquid SEDDS (at 40˚C ± 2˚C/ 75%RH ± 5%RH)

Test	After 1 month	After 2 months	After 3 months	After 6 months
Drug content (%)	98.44 ± 0.89	97.18 ± 0.25	97.05± 0.47	96.22 ± 0.89
Transmittance (%)	98.75 ± 1.05	97.44 ± 0.78	96.58 ± 0.77	95.47 ±0.47
Drug release (%)	96.11 ± 0.78	95.78 ± 0.47	94.59 ± 0.89	94.22 ±1.09

CONCLUSION

In this study, we successfully developed and evaluated a self-emulsifying drug delivery system for Nevirapine. Our optimization process identified Carbomer 940 C8 as the most soluble oil, with Cremophor RH 40 as the effective surfactant and PEG 400 as the co-surfactant. Early screening results demonstrated that these components achieved a remarkable transmittance exceeding 99% in aqueous solutions. Additionally, all prepared SEDDS formulations exhibited cloud points above 60°C, indicating thermal stability. The globule sizes within each formulation fell within the nanometric range, further affirming their stability. Notably, the F5 formulation exhibited a sustained drug release profile in 0.1N HCl, achieving 96.55% release within just 30 minutes. These findings underscore the significant enhancement in Nevirapine's release rate in the optimized F5 SEDDS formulation, suggesting its potential for improved therapeutic efficacy.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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