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FORMULATION AND EVALUATION OF SELF-EMULSIFYING DRUG DELIVERY SYSTEM (SED DS) FOR NEVIRAPINE

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ABSTRACT

This study focuses on the development and optimization of a self-emulsifying drug delivery system (SED DS) for Nevirapine, a BCS Class II non-nucleoside reverse transcriptase inhibitor (NNRTI) used in HIV therapy. Our objective was to significantly improve Nevirapine's oral bioavailability through a comprehensive in vitro dissolution study. We systematically assessed Nevirapine's solubility in various vehicles to identify the most effective component combinations. By using Chromophore RH40 as the surfactant, PEG400 as the co-surfactant, and Carbomer 940 as the oil phase, we created detailed pseudo-ternary phase diagrams. From this analysis, we selected eight formulations with Carbomer 940 at Smix ratios of 1:1, 2:1, and 3:1. The results indicate that the NEVIRAPINE-loaded SED DS demonstrate enhanced solubilization and nanosizing capabilities, effectively improving drug absorption and potentially leading to better therapeutic outcomes.

Keywords: Nevirapine, Self-emulsifying drug delivery system, Bioavailability, Solubility Enhancement.

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INTRODUCTION

Nevirapine, a non-nucleotide reverse transcriptase inhibitor, is used to treat HIV infection. Classified as a BCS class II medication, Nevirapine has high permeability but poor solubility. The oral route is the most traditional and practical method for administering therapeutic drugs, as it is easy to use, reduces therapy costs, and enhances patient compliance. However, the low water solubility of approximately 40% of new chemical entities presents a significant challenge for current medication delivery technologies. In many cases, solubilization in the gastrointestinal (GI) tract becomes the rate-limiting step for absorption. BCS class II medications, characterized by high permeability and poor water solubility, often encounter this issue [1-3].

Lipid-based drug delivery systems can improve the bioavailability of highly lipophilic substances by maintaining the medication in a dissolved state until absorption, thus overcoming the challenge of slow dissolution rates. These lipid formulations can range from simple oils to more complex combinations of co-solvents and surfactants.

Recent research has focused on microemulsion formulations, particularly self-emulsifying drug delivery systems (SED DS), to enhance the oral bioavailability of poorly water-soluble medications [4, 5].

To improve the therapeutic effects of these medications, alternative oral delivery routes must be developed. SED DS represent an intriguing approach to enhance the oral absorption, dissolution, and solubility of poorly water-soluble drugs. This research project primarily aims to develop an NEVIRAPINE-loaded SED DS suitable for oral administration to HIV patients [6-8].

MATERIALS AND METHOD

Nevirapine was purchased from a local pharma company Mass Pharma (Private) Limited, Cremophore RH40 was purchased from Sigma Aldrich. PEG 400 and Carbomer 940 were obtained from local market. Transcutol® P and Tween 80 were acquired from Gattefosse, France (Nanterre, France) and Sigma-Aldrich (St. Louis, MO, USA), respectively. All the substances were of analytical grade. Distilled water was used during the whole

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study.

Solubility Analysis

The solubility of nevirapine assessed in various oils, surfactants, and co-surfactants, including oleic acid, arachis oil, castor oil, soybean oil, isopropyl myristate, olive oil, and almond oil. Each mixture was prepared by adding an excess of the drug to two milliliters of the chosen solvent. The equilibrated mixture was then filtered and analyzed using a UV-visible spectrophotometer, with three measurements taken for each sample [9].

Preliminary Screening of Surfactants

To create a 1:1 combination of surfactant and oil, 100 mg each of Cremophore RH 40, Tween 80, and Span 20 were added to 100 mg of the oily phase. The percentage transmittance of the resulting mixture was measured at 638.2 nm using a UV spectrophotometer. The emulsions were also visually inspected for turbidity and phase separation [10].

Preliminary Screening of Co-surfactants

For the evaluation of co-surfactants, a ratio of 3:2:1 was maintained for oil, surfactant, and co-surfactant, respectively, achieving a 1:1 ratio of oil to surfactant/co-surfactant mixture. Mixtures were prepared containing 200 mg of surfactant, 100 mg of co-surfactant, and 300 mg of oil to further assess the emulsification capability of various co-surfactants [11-12].

Pseudo-ternary Phase Diagram Construction

Pseudo-ternary phase diagrams were constructed using the water titration method. The total concentrations of surfactant, co-surfactant, and oil for any composition were kept at 100%. Smix and oil were combined in a pre-weighed vial at specified surfactant to co-surfactant ratios of 1:1, 2:1, 3:1, and 1:2, with oil to Smix ratios of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1. The resulting mixtures were titrated with water dropwise until they formed easily flowable o/w microemulsions, which appeared either clear or slightly bluish. Systems that were less translucent and displayed a brilliant white or bluish-white color were classified as emulsions. To produce liquid SEDDS, the highest microemulsion region corresponding to the appropriate Smix value was identified and input into Design-Expert software version 8.

Preparation of Liquid Self-emulsifying Formulation

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 °C in a water bath to facilitate solubilization. The formulations were stored at room temperature until further analysis once their isotropicity was verified [12-15].

CHARACTERIZATION OF FORMULATIONS

Transmittance Testing

A UV-visible spectrophotometer measured transmittance to assess the stability of the SEDDS formulation upon dilution. Transmittance for each sample was recorded at 638.2 nm [16].

Self-Emulsification Time Calculation

Using the USP Dissolution Test Apparatus II, 1 ml of each formulation was added to 900 ml of distilled water and stirred continuously at 50 revolutions per minute at $37 \pm 0.5^\circ\text{C}$. The emulsification time, measured in seconds, indicated the duration required for the system to disperse evenly and completely.

Measurement of Cloud Points

Each formulation was placed in a water bath that was gradually heated and diluted with distilled water at a 1:250 ratio. The cloud point was defined as the temperature at which cloudiness began to appear.

Determination of Globule Size and Zeta Potential

The average droplet size, polydispersity index, and zeta potential of all gels were measured using a photon correlation spectrophotometer (Malvern Zetasizer). Gel samples were placed in cuvettes within a thermostatic chamber. Samples were diluted with distilled water prior to measurement [17].

Determination of Drug Content

Self-emulsifying formulations were dissolved in methanol. The resulting solution was filtered, and the absorbance was measured using a UV-Visible spectrophotometer. A diluted self-emulsifying formulation without the drug served as the blank at a wavelength of 263 nm [18].

In Vitro Dissolution Experiments

An in vitro release test was performed using a USP type-II dissolution apparatus with 900 mL of 0.1N HCl maintained at $37 \pm 0.5^\circ\text{C}$. Aliquots of 5 mL were taken at intervals, and each aliquot was replaced with fresh dissolving medium. After filtration through a membrane filter with a pore size of 0.45 μm , the analysis was conducted at 283 nm using a UV-Visible spectrophotometer [19, 20].

Stability Analysis

The stability test was conducted following ICH criteria. Evaluations included the appearance of the SEDDS, its self-emulsifying properties, transmittance, drug content, and percentages of drug release [21].

RESULTS AND DISCUSSION

The self-emulsifying drug delivery system (SEDDS) is an effective method for administering medications classified as class II and IV in the Biopharmaceutics Classification System (BCS), as it enhances the in vitro performance of poorly water-soluble drugs.

Study of Solubility

The solubility of a drug in excipients is crucial for the stability of the formulation, particularly since many formulations precipitate before in situ solubilization occurs. For a successful Nevirapine-loaded SEDDS formulation, it is essential that all of the Nevirapine dosage dissolves within the SEDDS components. The solubility of Nevirapine in various oils, surfactants, and co-surfactants. Among the examined vehicles, Carbomer 940 was identified as the oil phase with the highest solubilization capability whereas soyabean with minimum. PEG 400, with a better solubility was selected as the co-surfactant, while chemophore RH40 was used as the surfactant, demonstrating a good solubility.

Preliminary Assessment of Surfactants' Capacity for Emulsification

A well-formulated self-emulsifying drug delivery system (SEDDS) can dissolve within seconds when gently stirred. The sequence indicates the optimal order for achieving the highest emulsification efficiency, or maximum percentage transmittance, among the surfactants: Cremophor RH 40 > Tween 80 > Tween 20 > Span 20. Cremophor RH 40 demonstrated the highest transmittance rating, while Span 20 exhibited the lowest.

This study evaluated three co-surfactants: propylene glycol, transcitol, and PEG 400. When Carbomer 940 was used as the oil phase and Cremophor RH 40 as the surfactant, all co-surfactants showed favorable transmittance.

PEG 400 exhibited high transmittance of 94.45% followed by Cremophore RH40 (93.78%), tween 20 showed the least transmittance [22].

Pseudo-Ternary Phase Diagram

A simple pseudo-ternary phase diagram consists of three components: water, oil, and Smix. Each corner of the phase diagram represents 100% of each component. Carbomer 940 was chosen as the oil phase, with Cremophor RH 40 as the surfactant and PEG 400 as the co-surfactant to create distinct phase diagrams. The decisions regarding these components were informed by solubility studies and the initial screening of surfactants and co-surfactants.

The pseudo-ternary phase diagram, composed of Carbomer 940, Cremophor RH 40, and PEG 400 in different surfactant/co-surfactant different ratios was constructed using the water titration method. The shaded area represents the micro/nanoemulsion region, while the larger area indicates improved self-nanoemulsification capability.

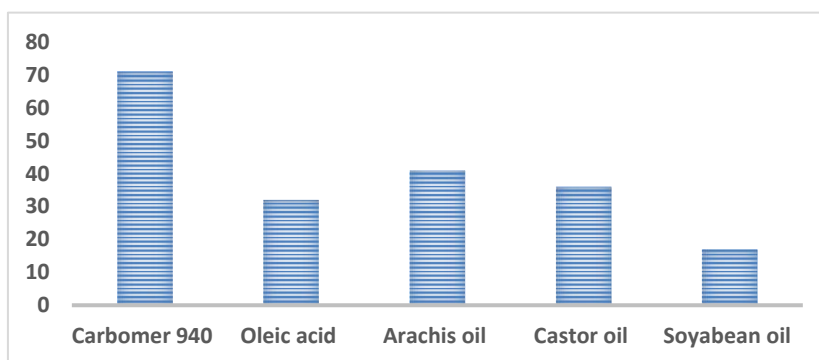


Figure 1: Solubility in various oils.

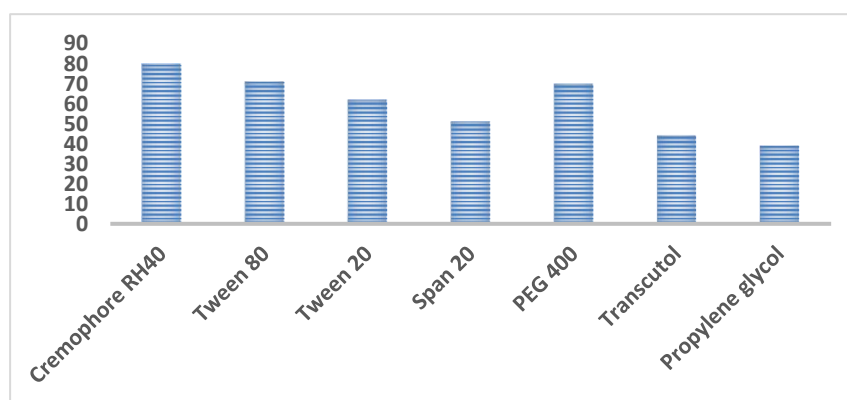


Figure 2: Solubilities in surfactants and cosurfactants.

Table 1: Characterization parameters of nevirapine-SEDSS formulations

Formulations	% Transmittance ± S.D.	Self-emulsification time (Sec) ± S.D.	Cloud Point (°C) ± S.D.	Globule size (nm) ± S.D.	Drug Content (%) ± S.D.
NS-1	96.53 ± 0.42	31.14 ± 0.27	63.6 ± 0.35	57.56 ± 0.28	95.42 ± 0.57
NS-2	97.65 ± 0.56	24.21 ± 0.35	65.2 ± 0.64	60.32 ± 0.29	95.34 ± 0.65
NS-3	94.61 ± 0.43	24.23 ± 0.56	69.1 ± 0.64	71.65 ± 0.11	97.54 ± 0.64
NS-4	97.42 ± 0.54	31.62 ± 0.10	70.2 ± 0.62	59.12 ± 0.41	99.55 ± 0.44
NS-5	98.48 ± 0.65	19.34 ± 0.31	71.1 ± 0.81	58.78 ± 0.57	98.61 ± 0.63
NS-6	96.45 ± 0.76	29.13 ± 0.42	68.2 ± 0.23	64.21 ± 0.44	96.24 ± 0.25
NS-7	95.83 ± 0.82	25.54 ± 0.57	71.6 ± 0.44	60.22 ± 0.65	96.43 ± 0.27
NS-8	97.49 ± 0.22	38.44 ± 0.32	70.1 ± 0.71	57.11 ± 0.33	97.25 ± 0.39
NS-9	96.71 ± 0.34	39.46 ± 0.21	66.2 ± 0.122	55.24 ± 0.53	97.37 ± 0.29

Determination of Self-Emulsification Time

The results for self-emulsification time are summarized in table 1. Formulations exhibited self-emulsification time of 19 -40 seconds.

Cloud Point Measurement

The cloud points of all SEDDS formulations were above 62-72 °C, as indicated in the table.

Globule Size Determination

The average size of formulation was 55-71 nm, which is the smallest among all formulations, as shown in the figure. The polydispersity index for the F5 formulation was calculated to be 0.144.

Zeta Potential Determination

The zeta potential of all SEDDS formulations ranged from -26.25 to -51.11 mV, indicating a stable system with well-separated emulsion globules [23-25].

Drug Content

The drug content in the selected SEDDS formulations ranged from 95-99%.

In-vitro Dissolution Studies

In-vitro dissolution tests were conducted using a USP type-II dissolving apparatus in 0.1 N HCl to compare drug release across various SEDDS formulations (F1-F8). The results are presented in the figures. After 30 minutes, the optimized formulation F5 demonstrated a maximum drug release of 96.55%. This indicates that the SEDDS formulation significantly enhanced the solubilization and release rate of Nevirapine [26-28].

Stability Study of F5 liquid SEDDS Formulation

The impact of stability conditions on the storage of the F5 formulation over six months was examined.

The percent transmittance (94-97%), drug content (96-99%), and drug release (93-96%) were not significantly reduced. The stability study concluded that the F5 formulation maintained its stability throughout the six-month period [29].

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 were within the nanometric range, further affirming their stability. Notably, the F5 formulation demonstrated a sustained drug release profile in 0.1N HCl, achieving a release of 96.55% within just 30 minutes. These findings highlight the significant enhancement in Nevirapine's release rate in the optimized F5 SEDDS formulation, suggesting its potential for improved therapeutic efficacy.

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