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FORMULATION AND EVALUATION OF SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEMS (SNEDDS) FOR EMPAGLIFLOZIN MATERIALS AND METHODS

Pentewar Ram Shankarrao, Sanket Dharashivkar, Rajeev Malviya

School of Pharmacy, Mansarovar Global University, Kolar Road, Bhopal (M.P.), India.

***Corresponding Author: Email:** rajeevrcp33@gmail.com

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ABSTRACT

The research focused on the development and evaluation of Efavirenz (EFZ)-loaded Liquid Self-Nanoemulsifying Drug Delivery Systems (L-SNEDDS) to improve the oral bioavailability of EFZ. Four different formulations were designed and optimized within a defined design space, focusing on key attributes such as self-emulsification time, robustness to dilution, droplet size, zeta potential, and in vitro drug release. The optimized formulation, SN3, exhibited rapid self-emulsification, excellent stability under stress conditions, and a favorable droplet size distribution in the nanoscale range. Zeta potential analysis indicated high colloidal stability, especially in the presence of 0.75% SLS solution. In vitro dissolution studies showed a significant improvement in drug release for SN3 compared to the market tablet formulation, indicating its potential to enhance EFZ oral bioavailability. The findings suggest that L-SNEDDS, particularly the SN3 formulation, could be a promising approach for the oral delivery of EFZ, addressing its solubility and bioavailability challenges.

Keywords – *Efavirenz, L-SNEDDS, self-emulsification, nanoemulsion, oral bioavailability, zeta potential.*

1. INTRODUCTION

Empagliflozin (EFZ), a potent sodium-glucose co-transporter 2 (SGLT2) inhibitor, is widely used in the management of type 2 diabetes mellitus due to its ability to lower blood glucose levels effectively. However, its clinical utility is significantly hampered by its poor solubility and bioavailability, which can lead to suboptimal therapeutic outcomes [1]. To address these limitations, innovative drug delivery systems, such as Self-Nanoemulsifying Drug Delivery Systems (SNEDDS), have been explored to enhance the solubility and absorption of poorly soluble drugs.

SNEDDS are isotropic mixtures of oil, surfactants, and co-surfactants that, when introduced into aqueous media, spontaneously form nano-sized emulsions. This technology has shown promise in improving the bioavailability of drugs with poor water solubility by facilitating enhanced drug dissolution and absorption [2]. The efficacy of SNEDDS depends on the careful selection of components, including lipids, surfactants, and co-surfactants, as well as the formulation's ability to self-emulsify under physiological conditions.

In this study, we aimed to formulate and evaluate SNEDDS for EFZ to improve its dissolution rate and pharmacokinetic properties. The approach involved screening various lipids, surfactants, and co-surfactants to identify the most effective components for SNEDDS formulation. Pseudoternary phase diagrams were used to determine the optimal ratios of these components, and several formulations

were prepared and tested for their ability to enhance the bioavailability of EFZ. The results of this study are expected to demonstrate the potential of SNEDDS technology in optimizing the delivery and therapeutic efficacy of poorly soluble drugs like EFZ.

2. MATERIALS AND METHODS

2.1 Materials

Empagliflozin was procured from Cipla Limited, Vikhroli, India. Other chemicals and reagents used were of analytical reagent grade.

2.2 Selection of SNEDDS Components

2.2.1 Screening of Lipids

The solubility of Empagliflozin in various lipids was assessed to select appropriate lipid vehicles. Excess Empagliflozin was added to a defined volume of each lipid and mixed for 48 hours using a vortex mixer (SPINIX-Vortex Shaker) at room temperature (25±2°C). The mixtures were centrifuged at 3,000 rpm for 10 minutes with a Remi-RMI centrifuge, and undissolved drug was removed via filtration through a 0.22 μm membrane filter. The resulting solutions were diluted with methanol, and the concentration of Empagliflozin was measured using a validated UV method at 290 nm with a double beam UV-VIS spectrophotometer (Kaur et al., 2015). This procedure was performed in triplicate [3,4].

2.2.2 Screening of Surfactants

Surfactants were screened based on their ability to dissolve Empagliflozin and their emulsification efficiency. Empagliflozin's solubility in surfactants (Kolliphor® RH40, Labrasol®, Tween® 20, Tween® 60, Tween® 80, Span® 20, Span® 80) was determined using the same method as for lipids. Surfactants with higher solubility were tested for emulsification efficiency by adding 1 mL of each surfactant to 1 mL of selected lipid, heating at 50°C, and mixing. The emulsification was assessed by the number of inversions required to form a nanoemulsion and by measuring the percentage transmittance (%T) at 650 nm using a UV-VIS spectrophotometer (UV-1800, Shimadzu, Japan) (Gurjeet Kaur et al., 2013). Visual inspection for turbidity and phase separation was also conducted [5].

2.2.3 Screening of Cosurfactants

Cosurfactants (glycerol, PEG 400, PEG 600, propylene glycol, and Transcutol® HP) were screened based on their emulsification efficiency in a lipid-surfactant system. The emulsification was evaluated by the number of inversions required to create a nanoemulsion and by %T of the resulting emulsion. Cosurfactants were selected also based on Empagliflozin's solubility in these cosurfactants, determined using the same method as for lipids and surfactants (Nasr et al., 2016; Date & Nagarsenker, 2007) [6].

2.3 Construction of Pseudoternary Phase Diagrams

Pseudoternary phase diagrams were constructed using the water titration method at 25±2°C (Azeem et al., 2009). Different proportions of surfactant and cosurfactant (Smix) were mixed and titrated with water. The phase diagrams were created using Tri-plot software by plotting the end points of titration [7].

2.4 Preparation of Empagliflozin-loaded SNEDDS

Based on the pseudoternary phase diagrams, four SNEDDS formulations (SN1, SN2, SN3, and SN4) were prepared by varying the proportion of oil (Capmul® MCM) and Smix (Kolliphor® RH40 and PEG 600 in a 3:1 ratio). Each formulation was loaded with 100 mg of Empagliflozin per mL of SNEDDS. The preparation involved mixing Capmul® MCM with Smix31 and adding Empagliflozin to the mixture under stirring until fully dissolved (Patel et al., 2016) [8].

2.5 Evaluation of Empagliflozin-loaded SNEDDS

2.5.1 Self-emulsification Time: The ability of SNEDDS to self-emulsify was assessed by adding 1 mL of SNEDDS to 250 mL of distilled water at 37°C under gentle stirring. The time required for the disappearance of SNEDDS and appearance of the nanoemulsion was recorded, and %T was measured at 650 nm (Patel et al., 2011) [9].

2.5.2 Robustness to Dilution: The formulations were diluted 10, 100, and 1000 times with distilled water, 0.1 N HCl, and phosphate buffers (pH 6.8 and 7.4). They were stored for 24 hours and examined for phase separation or precipitation (Nasr et al., 2016) [10].

2.5.3 Droplet Size and Zeta Potential: Particle size and zeta potential of the nanoemulsions were measured using a Malvern Zetasizer by diluting SNEDDS formulations to 1000 mL with distilled water and 0.75% SLS solution (Reddy & Sowjanya, 2015; Czajkowska-Kosnik et al., 2015) [11].

2.5.4 Thermodynamic Stability Testing: Stability was evaluated through heat-cool cycles, centrifugation, and freeze-thaw cycles. Formulations were subjected to six heat-cool cycles (4°C and 45°C), centrifugation at 3500 rpm, and three freeze-thaw cycles (-21°C and +25°C) (Nasr et al., 2016; Reddy & Sowjanya, 2015) [12].

2.5.5 Drug Content: Empagliflozin content was determined by diluting 1 mL of SNEDDS (equivalent to 100 mg of Empagliflozin) with methanol, mixing, and measuring absorbance at 290 nm using a UV-VIS spectrophotometer (Shimadzu UV-1800) [13].

2.5.6 In Vitro Drug Dissolution Study: SNEDDS formulations were filled into hard gelatine capsules (size "00") and dissolution rates were determined using a standard dissolution test method, with measurements taken in triplicate (Abd-Elhakeem et al., 2019).

3. RESULTS AND DISCUSSION

3.1 Screening of Lipids

The solubility of the active pharmaceutical ingredient (API) in the lipid phase is a crucial criterion for selecting appropriate lipids for self-nanoemulsifying drug delivery systems (SNEDDS) (Porter et al., 2007). High solubility of the drug in the lipid phase facilitates efficient drug loading and enables the preparation of a low-volume formulation. The solubility of Empagliflozin (EFZ) in various lipids, determined at room temperature (RT, 25 ± 0.5 °C), is presented in Table 1 and Figure 1.

EFZ exhibited the highest solubility in Capmul® MCM (198.93 ± 6.13 mg/mL), followed by Capryol™ 90 (89.38 ± 0.53 mg/mL). The lowest solubility was observed in peanut oil (0.69 ± 0.08 mg/mL). Notably, the solubility of EFZ in Capmul® MCM was nearly double the intended dose of 10 mg per millilitre, highlighting its significant potential for drug solubilization.

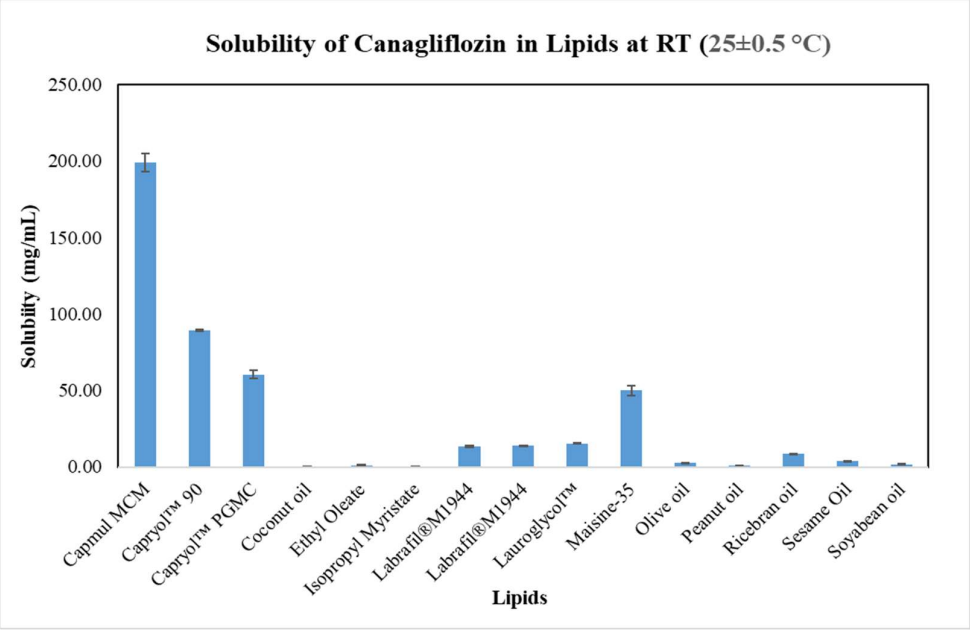


Fig. 1: Solubility of EFZ in Lipids

Table 1: Solubility of Empagliflozin in Lipids

Sr. No.	Lipid/Oil	Solubility (mg/mL ± SD) (n=3)
1	Capmul® MCM	198.93 ± 6.13
2	Capryol™ 90	89.38 ± 0.53
3	Capryol™ PGMC	65.47 ± 2.43
4	Coconut oil	0.52 ± 0.01
5	Ethyl Oleate NF	2.11 ± 0.16
6	Isopropyl Myristate	0.35 ± 0.01
7	Labrafil® M1944	15.43 ± 0.45
8	Labrafil® M2125	15.86 ± 0.05
9	Lauroglycol™	12.33 ± 0.40
10	Maisine 35-1	39.13 ± 3.24
11	Olive oil	1.88 ± 0.09
12	Peanut oil	0.49 ± 0.08
13	Rice bran oil	6.56 ± 0.32
14	Sesame oil	2.75 ± 0.11
15	Soybean oil	1.50 ± 0.23

The high solubilizing potential of Capmul® MCM for EFZ suggests its suitability as the lipid component in the proposed SNEDDS formulation. This lipid's efficacy can be attributed to its composition as a mono-diglyceride of medium-chain fatty acids (primarily caprylic and capric acids), which enhances its ability to dissolve the lipophilic EFZ (log P = 3). Additionally, Capmul® MCM's status as a Generally Recognized as Safe (GRAS) substance further supports its selection for the formulation.

3.2 Screening of Surfactants

The solubility of Empagliflozin (EFZ) in various surfactants is summarized in Table 2 and Figure 2. Kolliphor® RH 40 demonstrated the highest solubility, with 471.93 ± 1.90 mg/mL of EFZ, followed by Labrasol® (365.33 ± 3.51 mg/mL), Tween 80 (51.77 ± 3.06 mg/mL), and Tween 20 (50.93 ± 2.66 mg/mL). Span 80 showed the lowest solubility, with only 14.84 ± 1.14 mg/mL.

The top four surfactants, which exhibited the highest solubility for EFZ, were further evaluated for their emulsification efficiency in Capmul® MCM. Emulsification efficiency was assessed in terms of percentage transmittance (%T) and the number of flask inversions required to achieve a homogeneous emulsion. These results are presented in Table 2 and Figure 2.

Kolliphor® RH 40 achieved the highest emulsification efficiency, with a %T of 97.71 ± 1.21% and required 12 flask inversions. In comparison, Labrasol®, Tween 20, and Tween 80 required fewer inversions (11 ± 0.82, 8 ± 0.82, and 4 ± 0.82, respectively), but their %T values were significantly lower (1.20 ± 0.21%, 32.18 ± 0.34%, and 12.18 ± 1.06%, respectively).

Table 2: Solubility of Empagliflozin in Surfactants

Sr. No.	Surfactant	Solubility (mg/mL ± SD) (n=3)
1	Kolliphor® RH 40	471.93 ± 1.90
2	Labrasol®	365.33 ± 3.51
3	Tween 20	50.93 ± 2.66
4	Tween 60	18.54 ± 1.01
5	Tween 80	51.77 ± 3.06
6	Span 20	6.50 ± 0.36
7	Span 80	14.84 ± 1.14

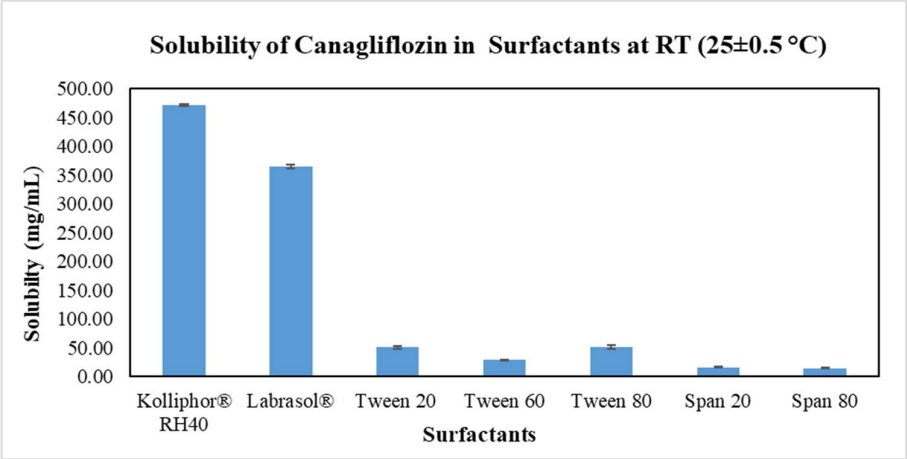


Fig. 2: Solubility of Empagliflozin in Surfactants

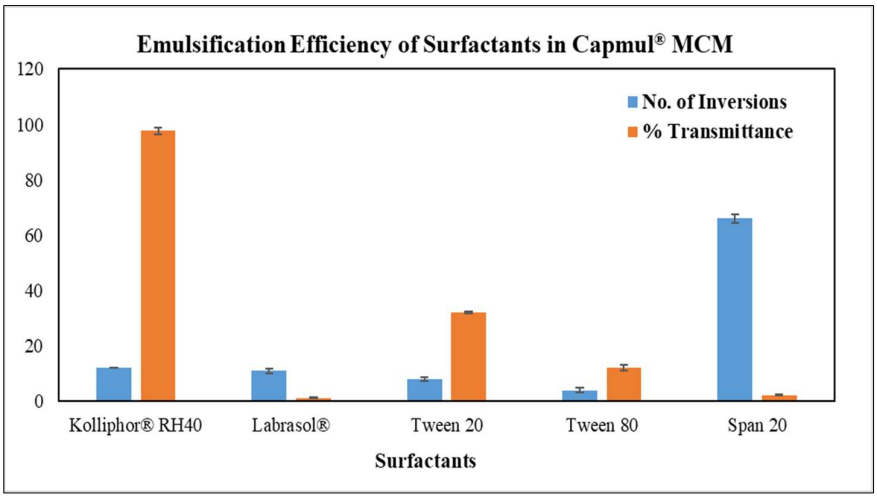


Fig. 3: Emulsification Efficiency of Surfactants with Capmul® MCM

Table 3: Emulsification Efficiency of Surfactants in Capmul® MCM

Surfactant	Number of Inversions	%T ± SD
Kolliphor® RH 40	12	97.71 ± 1.21
Labrasol®	11	1.20 ± 0.21
Tween 20	8	32.18 ± 0.34
Tween 80	4	12.18 ± 1.06

The results indicate that Kolliphor® RH 40 not only has the highest solubilizing capacity for EFZ but also shows the best emulsification efficiency with Capmul® MCM, as evidenced by the highest %T and the lowest number of inversions. This superior performance can be attributed to Kolliphor® RH 40 being a polyoxyethylene castor oil derivative, a complex mixture of hydrophobic and hydrophilic components, with an HLB value between 14 and 16. This property enables the formation of fine emulsion droplets, which facilitates rapid drug release and absorption. Additionally, its non-ionic nature ensures safety and biocompatibility. Therefore, Kolliphor® RH 40 was selected as the surfactant component for the SNEDDS formulation.

3.3 Screening of Co-Surfactants

The inclusion of a co-surfactant in the formulation is known to enhance the dispersibility and absorption of the drug. In this study, five co-surfactants—glycerol, PEG 400, PEG 600, propylene glycol, and Transcutol® HP—were evaluated for their emulsification efficiency in a system containing Capmul® MCM and Kolliphor® RH 40. The emulsification efficiency of these co-surfactants was assessed by measuring the percentage transmittance (%T) of the resulting nanoemulsions, as detailed in Table 4 and Figure 4.

All co-surfactants demonstrated similar performance, with %T values exceeding 95%, indicating high emulsification efficiency. The number of inversions required to form a homogeneous emulsion varied slightly among the co-surfactants, with results shown in Table 4.

Table 4: Emulsification Efficiency of Co-Surfactants in Capmul® MCM-Kolliphor® RH 40 Systems

Sr. No.	Co-Surfactant	Number of Inversions ± SD (n=3)	% Transmittance ± SD (n=3)
1	Glycerol	18 ± 0.82	87.04 ± 0.59
2	PEG 400	21 ± 0.00	85.02 ± 0.77
3	PEG 600	15 ± 0.00	88.53 ± 0.62
4	Propylene Glycol	15 ± 0.82	84.23 ± 1.96
5	Transcutol® HP	16 ± 0.82	85.88 ± 0.46

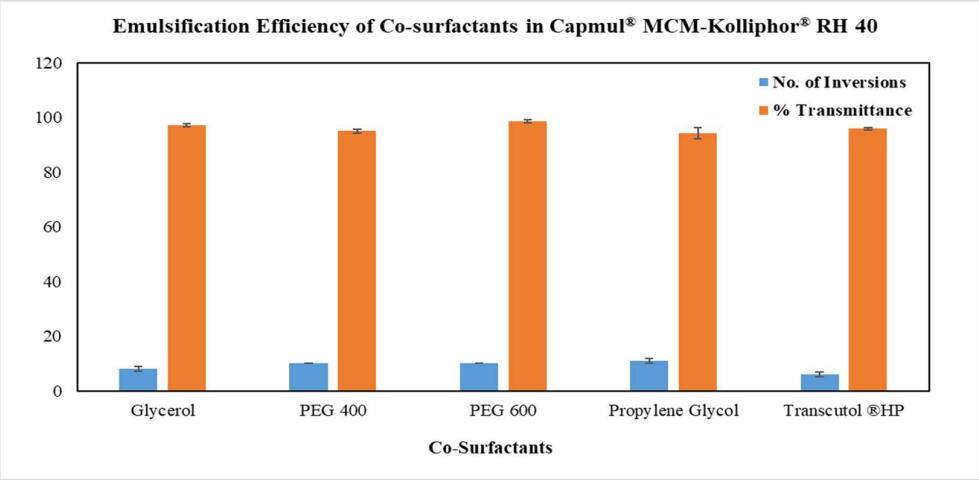


Fig. 4: Emulsification Efficiency of Co-Surfactants in Capmul® MCM-Kolliphor® RH 40 Systems

To evaluate whether the observed differences in %T were statistically significant, an analysis of variance (ANOVA) was conducted, followed by Tukey's Honest Significant Difference (HSD) test, using the online statistical tool VassarStats: Statistical Computation Web Site.

Additionally, the solubilizing capacity of each co-surfactant for EFZ was assessed. Results, presented in Table 5 and Figure 5, indicated that glycerol exhibited the lowest solubilizing capacity (59.17 ± 0.76 mg/mL) compared to PEG 600 (206.61 ± 4.26 mg/mL) and Transcutol® HP (525.00 ± 4.36 mg/mL). Based on these solubility results, glycerol was excluded from further consideration.

Table 5. Solubility of Empagliflozin in Co-Surfactants

Sr. No.	Co-Surfactant	Solubility (mg/mL ± SD) (n=3) (RT = 25 ± 0.5 °C)
1	Glycerol	59.17 ± 0.76
2	PEG 400	222.93 ± 1.84
3	PEG 600	206.61 ± 4.26
4	Propylene Glycol	346.47 ± 1.55
5	Transcutol® HP	525.00 ± 4.36

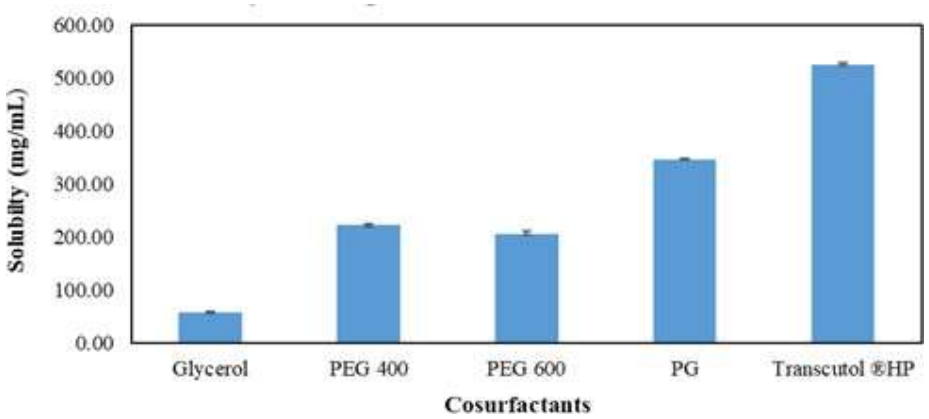


Figure 5. Solubility of Empagliflozin in Co-Surfactants

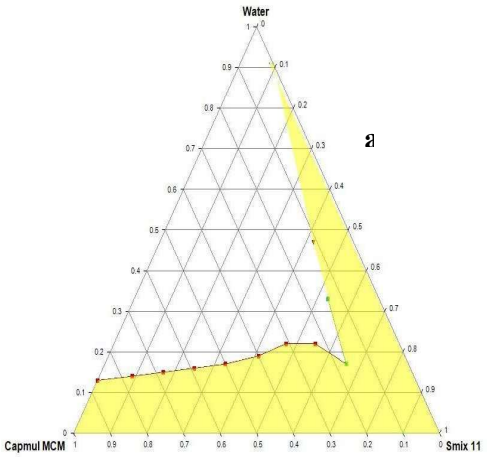
During the solubility studies, a red discoloration was observed in the EFZ solution containing Transcutol® HP, a phenomenon not seen with any other co-surfactant. This discoloration is depicted in Figure 5, along with a comparative image of EFZ in PEG 600.

Based on the solubility and visual observations, PEG 600 was selected over Transcutol® HP as the co-surfactant for the Capmul® MCM-Kolliphor® RH 40 system.

Thus, the final components selected for the formulation of the proposed EFZ SNEDDS were Capmul® MCM as the lipid, Kolliphor® RH 40 as the surfactant, and PEG 600 as the co-surfactant.

3.4 Construction of Pseudo-Ternary Phase Diagram

Pseudo-ternary phase diagrams were constructed to identify the self-emulsifying regions and optimize the concentration of Capmul® MCM (oil), Kolliphor® RH 40 (surfactant), and PEG 600 (co-surfactant) in the SNEDDS preconcentrate. These diagrams help determine the appropriate proportions of SNEDDS components to achieve nanoemulsion formation upon aqueous dilution. The data from aqueous titrations are summarized in Tables 6a to 6e, with the corresponding phase diagrams, constructed at surfactant/co-surfactant ratios (Smix) of 1:1, 1:2, 1:3, 2:1, and 3:1, presented in Figures 27a-27e.



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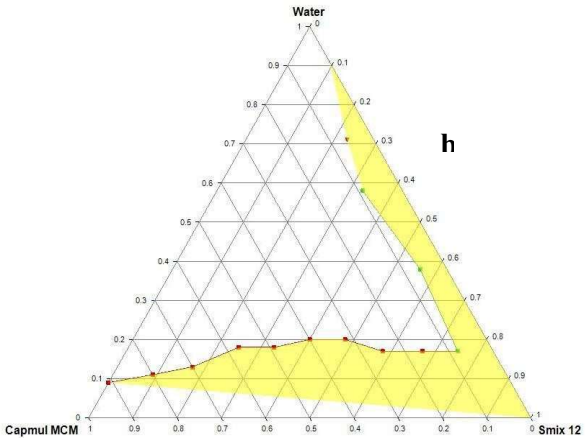

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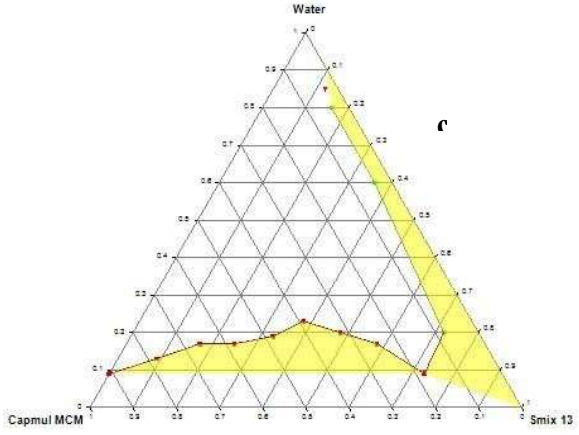

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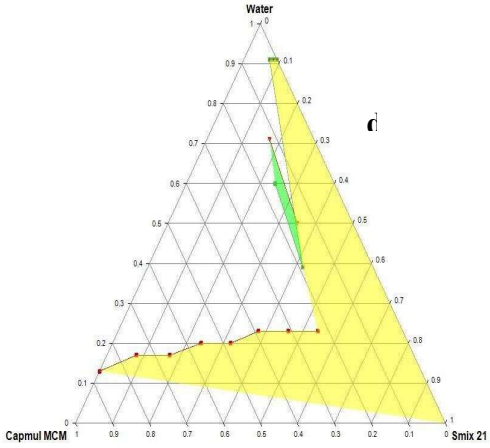

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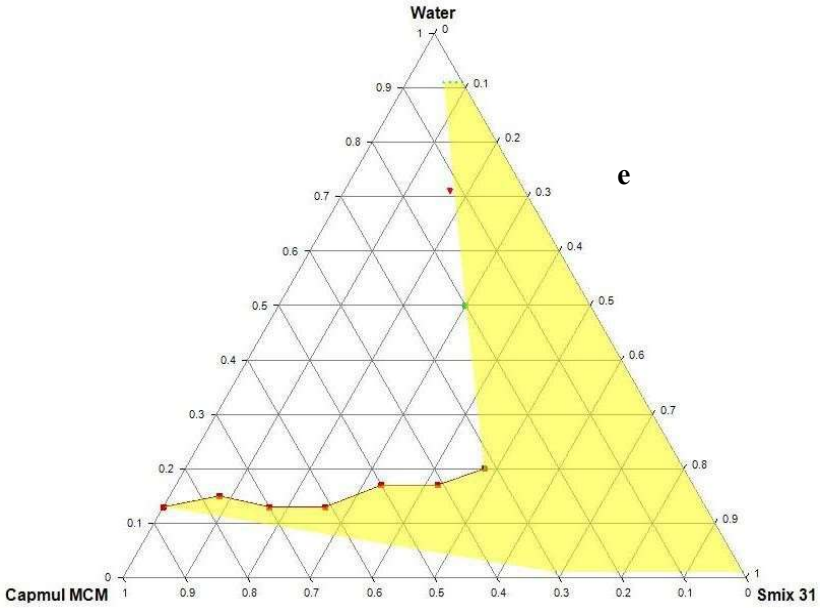

Figure 6 a-e. Pseudo-Ternary Phase Diagrams Prepared by Aqueous Titration of Placebo SNEDDS

In each of these diagrams, the shaded area represents the nanoemulsifying region, where clear and transparent systems were observed during aqueous titration, based on visual inspection. The remaining portions indicate the emulsion region and metastable systems, which were not considered for further study.

As the Smix ratio was adjusted from 1:1 to 3:1, reducing the proportion of the co-surfactant in the surfactant-cosurfactant mix, the nanoemulsifying region became wider. This wider region signifies better nanoemulsifying efficacy. Therefore, the phase diagram prepared with an Smix ratio of 3:1 was selected for further studies.

3.5 Preparation of EFZ-Loaded SNEDDS Based on Design Space

According to the International Conference on Harmonisation (ICH) guidelines, quality is defined as "the suitability of either a drug substance or drug product for its intended use" (ICH Expert Working Group, 2009). In this research, SNEDDS were designed to enhance the dissolution rate and bioavailability of EFZ. For the EFZ-loaded SNEDDS to exhibit these properties, they must form a stable nanoemulsion upon dilution with an aqueous medium (Patel et al., 2016).

To ensure this, a design space was identified within the center of the nanoemulsifying area. The formulation developed from this region would result in a nanoemulsion with droplet sizes in the nano range upon contact with an aqueous phase with mild agitation (Beg et al., 2015). This rapid drug release and higher absorption across the gastrointestinal tract are crucial for the desired therapeutic effect. The design space is marked in blue in Figure 7 within the Smix 3:1 phase diagram.

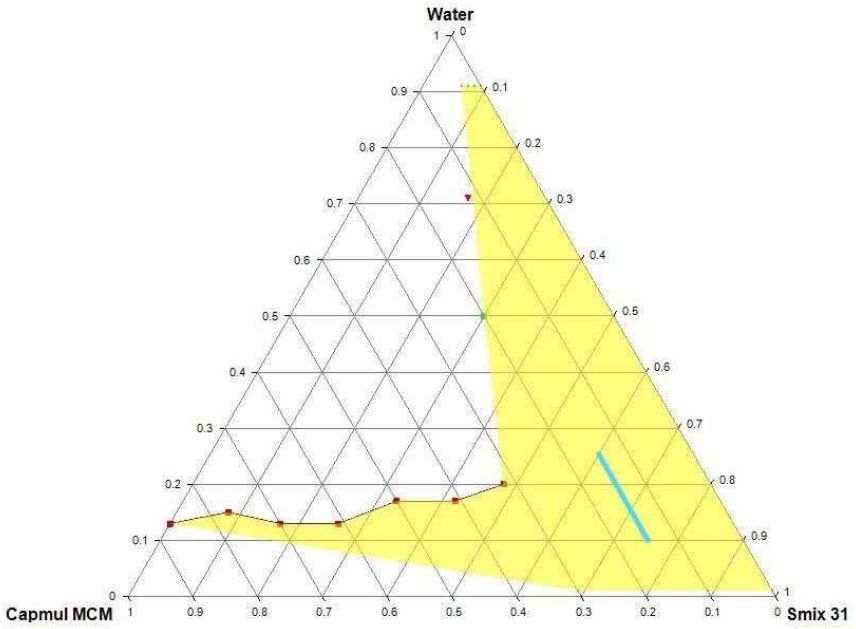

Figure 7. Design Space (Shown in Blue) in Pseudo-Ternary Phase Diagram

3.6 Evaluation of EFZ-Loaded Liquid SNEDDS

Four formulations were prepared to validate the defined design space and were evaluated for various parameters. The results of these evaluations are summarized below:

3.6.1 Self-Emulsification Time

The primary method for assessing self-emulsification in SNEDDS is visual estimation, particularly by determining the rate of emulsification, which indicates the efficiency of the process. The SNEDDS should disperse completely and rapidly upon aqueous dilution under mild agitation, similar to conditions in the gastrointestinal tract (GIT) (Augustine et al., 2016; Parmar et al., 2011). The emulsification time study results, showing that the formulations emulsified within 10 seconds, indicating a rapid process.

3.6.2 Robustness to Dilution

Table 28 shows the robustness to dilution results, indicating that none of the SNEDDS formulations exhibited phase separation or precipitation upon dilution with any of the aqueous media. This suggests that these SNEDDS formulations are stable at infinite aqueous dilution, with the composition and pH of the aqueous phase having no effect on the properties of the resulting nanoemulsions (Li et al., 2005; Kallakunta et al., 2012).

3.6.3 Thermodynamic Stability Test

Samples were considered to have passed (P) the test if no signs of phase separation or precipitation were observed, while those with signs of instability failed (F). All EFZ-loaded SNEDDS formulations showed no signs of instability under stress conditions, indicating that they were stable.

3.6.4 Droplet Size and Zeta Potential Determination

Droplet size is crucial in SNEDDS performance as it influences drug release and absorption. Systems with a mean droplet size below 200 nm meet SNEDDS criteria (Nasr et al., 2016). Smaller globule sizes were observed in the presence of SLS due to further reduced interfacial tension, stabilizing the new surfaces. The decrease in droplet size with increased Smix proportion suggests a more stable and condensed surfactant film at the oil-water interface.

Zeta potential determination further indicated the stability of the colloidal system. Higher negative zeta potential values suggest a stable dispersion, while low values indicate potential instability.

The results showed that SNEDDS formulations diluted with water had zeta potential values ranging from -3.25 mV to -8.95 mV, while those diluted with 0.75% SLS had values from -80.8 mV to -51.8 mV. The low zeta potential in water was due to the non-ionic surfactants, while the higher negative values in SLS were attributed to the anionic nature of SLS.

3.6.5 Drug Content

Table 34 presents the amount of EFZ estimated in 1 mL of L-SNEDDS formulations. Each milliliter of the formulation contained 100 mg of EFZ, with 100% drug loading efficiency, reflecting the high potential of L-SNEDDS as a monophasic pre-concentrate that solubilizes the drug in a single-phase system.

3.6.6 Cloud Point Measurement

Cloud point is a critical characteristic for systems intended for oral administration, where phase separation occurs if the temperature exceeds a certain limit, affecting drug absorption.

3.6.7 In Vitro Dissolution Studies

In vitro drug dissolution studies are crucial for assessing the release profile of SNEDDS formulations. Dissolution profiles of EFZ-loaded SNEDDS formulations was carried out in 0.1N HCl and 0.75% SLS, respectively. Formulation SN3 showed the most promising release profile, achieving almost complete drug release within 20 minutes.

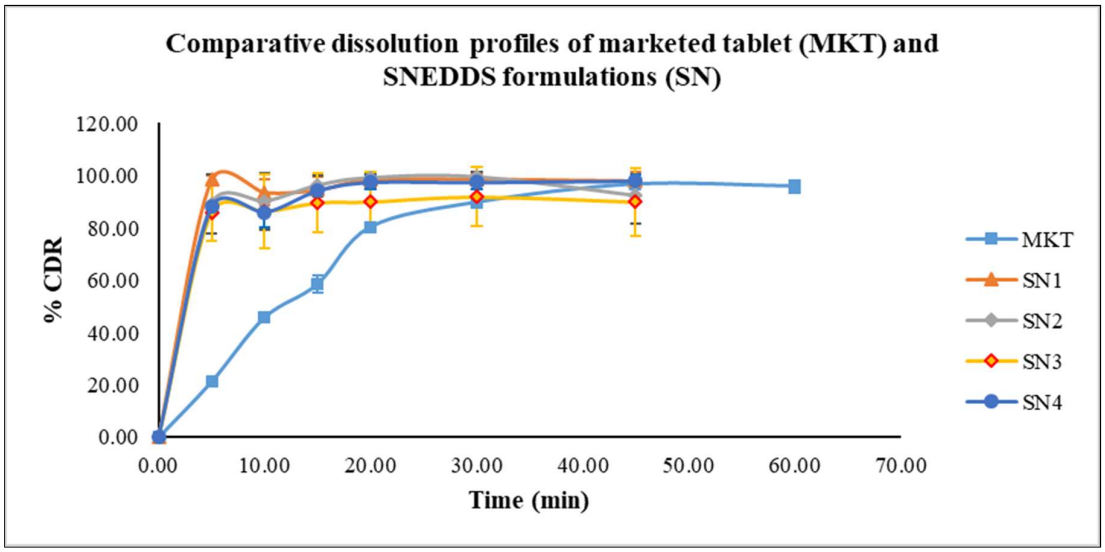

Fig. 8 : Comparative dissolution profiles of MKT and L-SNEDDS formulations

The solubility of EFZ in various lipids, surfactants, and cosurfactants was evaluated to select the optimal components for SNEDDS formulation. Capmul® MCM demonstrated the highest solubility for EFZ among the tested lipids [15]. Kolliphor® RH 40 exhibited the highest solubilizing and emulsification efficiency among the surfactants, making it a suitable choice for the formulation. PEG 600 was selected as the co-surfactant based on its emulsification efficiency and solubilizing capacity [16].

Pseudoternary phase diagrams revealed the self-emulsifying regions, and SNEDDS formulations were prepared using the optimized ratios of lipid, surfactant, and cosurfactant. The formulations demonstrated rapid self-emulsification and stability under various conditions. The in vitro dissolution studies indicated a significant improvement in the dissolution rate of EFZ from the SNEDDS formulations compared to the pure drug.

4. CONCLUSION

The development and evaluation of Efavirenz (EFZ)-loaded Liquid Self-Nanoemulsifying Drug Delivery Systems (L-SNEDDS) demonstrated significant potential for enhancing the oral bioavailability of EFZ. The SNEDDS formulations were meticulously designed and optimized to ensure rapid emulsification, stability under various stress conditions, and efficient drug release. Among the four formulations tested, SN3 (comprising a 2:8 ratio of Capmul® MCM to Smix) stood out as the most promising.

This formulation exhibited rapid self-emulsification within 10 seconds, produced a clear and transparent nanoemulsion, and showed no signs of phase separation or precipitation across a wide range of dilution media. The droplet size distribution was well within the desired nanoscale range, particularly in the presence of 0.75% SLS, indicating a stable and finely dispersed system. The zeta potential values further confirmed the colloidal stability of the formulations, with higher negative values indicating robust stability in the presence of anionic surfactants.

The cloud point measurement indicated that the formulation would remain stable at physiological temperatures, and the in vitro dissolution studies revealed an excellent drug release profile, with nearly complete release within 20 minutes. SN3 achieved the highest dissolution efficiency, making it a strong candidate for improving the oral delivery of EFZ.

Overall, this research highlights the effectiveness of L-SNEDDS as a novel delivery system for EFZ, with the potential to overcome the limitations associated with its poor solubility and bioavailability. The optimized SN3 formulation warrants further investigation and development, potentially leading to more effective and patient-friendly EFZ-based therapies.

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