Preparation and statistical optimization of self nanoemulsifying tablets of Efavirenz using $2^3$ factorial designs

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Abstract

The objective of the present research was to enhance the solubility of poorly water soluble antiretroviral drug i.e. efavirenz, by self nanoemulsifying drug delivery system (SNEDDS) and formulating it as tablets using $2^3$ factorial designs. The SNEDDS were prepared using labrafac PG (15%) as oil, Tween 80 (19%) as surfactant and PEG 200 (38%) as co surfactant that yields the globule size of 142.7nm. The liquid SNEDDS were adsorbed onto aerosil which acts as carrier. The SEM of S-SNEDDS appeared as smooth-surfaced particles without any crystalline shape, indicating complete adsorption of SNEDDS. The absence of drug peak in S-SNEDDS thermogram was attributable to presence of drug in molecularly dissolved state in the vicinity of the lipid excipients. The $2^3$ factorial designs were employed to optimize the concentration of Micro crystalline cellulose, PVP and sodium starch glycollate. The observed values were in close agreement with the predicted values thereby validating the feasibility of the optimization procedure in developing self nanoemulsifying tablets. The relative bioavailability of the S SNEDDS and pure drug were 388.49% and 95.39%, respectively. This confirms that the solubility of the drug has been increased leading to increase in the bioavailability of efavirenz.

Keywords: Self nanoemulsifying drug delivery system, $2^3$ factorial designs and bioavailability.

Introduction

Human Immunodeficiency Virus (HIV) a causative agent for Acquired Immuno deficiency Syndrome (AIDS) an immuno compromised condition that continues to be a frightening exterminator till date and more than 33 million people were affected worldwide [1]. Prevention of HIV infection to reduce the number of newly infected individuals is an international priority [2]. The main hindrances for highly compliant pharmacotherapy were less number of ARVs approved by the regulatory agencies and poor solubility profile [3]. Efavirenz belongs to the class of non-nucleoside reverse transcriptase inhibitors that inhibits non-competitively human HIV-1 reverse transcriptase [4]. Efavirenz belongs to BCS class 2 drug that has poor solubility and high permeability. The dissolution rate of the drug depends on aqueous solubility of a drug. The poor dissolution rate soaring from low solubility often results in the low bioavailability of orally administered drugs[5]. In order to achieve required therapeutic plasma concentrations after oral administration, poorly water soluble drugs usually requires high doses [6]. To improve the aqueous solubility various formulation strategies were reported in the literature including the use of surfactants, micronization, cyclodextrins, solid dispersions, permeation enhancers and lipids [7]. Self nanoemulsifying drug delivery systems (SNEDDS) are mixtures oil, surfactants, cosurfactants that form fine oil in water nanoemulsions when introduced into aqueous phases under gentle agitation [8]. After the successful development of Neoral Sandimmun the development of lipid formulations, especially SNEDDS, has received increased attention [9]. Due to high patient compliance, relatively easy to produce, easy to market, accurate dosing, good physical and chemical stability makes solid dosage forms like tablets and capsules were the most popular and preferred drug delivery forms. The prepared SNEDDS were formulated as tablets to get the advantage of improved solubility as well as to add the advantages of tablet [10]. Traditional experimentation approach on new pharmaceutical formulations development involves significant amount of time, materials and efforts to get valid results for a complex system. The major drawback of traditional experimentation also consequently associated with high cost, due to the existence of multiple factors that affects the formulation performance and manufacturing process. Recently, design of experiment (DOE) supported by statistical software has been reported as an efficient and powerful tool in the development and optimization of pharmaceutical dosage forms [11]. Factorial design is an efficient method of finding the relative significance of multiple variables and their interaction on the response or outcome of the study [12]. In the current research work, a three factor, two levels ($2^3$) full factorial design was used to

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optimize the concentrations of diluent, binder and disintegrant on the responses hardness, disintegration time and dissolution.

**Materials and Methods**

**Materials**

Efavirenz was provided as a gift sample from Shasun labs (Pondicherry, India). Labrafac PG was generous gift from Gattefosse, France (through Bombay College of Pharmacy, Mumbai). Porous Polystyrene beads were obtained as gift sample from Thermax Limited (Pune, India). Accurel was obtained from Membrana (Obernburg, Germany). Tween 80, PEG 200, MCC, sodium starch glycolate and polyvinylpyrollidone purchased from Loba chemie Pvt Ltd, Mumbai. All other chemicals and buffers used were of analytical grade.

**Preparation of Liquid SNEDDS**

Based on the preliminary studies (solubility studies, pseudoternary phase diagram and thermodynamic stability study) a self nano emulsifying system of efavirenz was prepared using labrafac PG as oil, Tween 80 as surfactant and PEG 200 as co surfactant [13]. The preparation of the SNEDDS contains the following steps:

1. 50mg of efavirenz was selected as the dose for incorporation into the oil phase.
2. The surfactant and co surfactant was added to the oil phase and mixed with magnetic stirrer.
3. Equilibrating in room temperature for 24hr before use.

**Preparation of Solid SNEDDS**

Aerosil, accurel MP 1000 and porous polystyrene spheres were used as the solid adsorbents to load efavirenz SNEDDS. The lipid formulation was added in increments and blended with the adsorbent at the following fixed efavirenz SNEDDS to adsorbent ratios by weight. Briefly, a constant aliquot of efavirenz SNEDDS was initially added to and mixed with the adsorbent in a mortar. The addition of lipid was suspended when non flowing mass is formed. The obtained mass was passed through 250 μm mesh to get uniformity in particle size. The flow behavior and loading efficiency of the adsorbed blend was then analyzed. The powder samples were stored in a desiccator until further evaluation. [14]

**Characterization of solid SNEDDS**

**Scanning Electron Microscope**

The surface morphology of Solid SNEDDS was examined by scanning electron microscope (Hitachi S3400, Tokyo, Japan). The powder samples were glued and mounted on metal sample plates. After this the samples were gold coated with a sputter coater using an electrical potential of 2.0 kV at 25 mA for 10 min[15].

**Differential Scanning Calorimetry**

The physical state of drug in solid SNEDDS was characterized by the differential scanning calorimetry thermogram analysis. The samples (about 3.00 mg) were placed in standard aluminum pans, and dry nitrogen was used as effluent gas. All samples were scanned at a temperature ramp speed of 5 C/min and the heat flow from 0 to 200 C [16].

**Reconstitution properties of solid SNEDDS**

The mean globule size and polydispersity index (P.I.) of the resulting nanoemulsions were determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zetasizer 3000 (Malvern Instruments Worcestershire, UK) Light scattering was monitored at 25°C at a 90°angle.

**Experimental design**

The 2^3 full factorial designs were carried out systematically with three factors at two levels to prepare the efavirenz loaded SNEDDS tablets. A total of eight experimental trials were done at all possible combinations. Venturing taken during optimization of excipient the amount of MCC (A), PVP (B), and the amount of sodium starch glycolate (C) were selected as the independent variables that were varied at two levels (low and high). The levels of the variables studied were chosen so that their relative divergence was capable to have a quantifiable effect on the response, along with the information that the selected levels are within practical use [17, 18]. The responses (dependent variables) selected for the study were hardness, disintegration and cumulative drug release at 40 min. The statistical experimental design was generated and evaluated using Design-Expert 8.0.6.1 software (Stat-Ease Inc., USA). The independent variables with its levels and the responses were shown in Table 1.

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: MCC</td>
<td>200.00, 300.00</td>
</tr>
<tr>
<td>B: PVP</td>
<td>12.00, 20.00</td>
</tr>
<tr>
<td>C: SSG</td>
<td>8.00, 16.00</td>
</tr>
</tbody>
</table>

**Preparation of tablets**

The archetypal formula for preparation of efavirenz loaded SNEDDS tablet used in this study was given in Table 2. Tablets were punched by direct compression of mixtures on a B2 rotary tablet press (Remak, Ahmedabad) with flat plane face punches (punch diameter = 12mm) at 50 rpm. The excipients were screened through a #20 mesh. The final mixture to be compressed was prepared by mixing in a polyethylene bag manually for 10min. finally lubricant was added to this blend and motley properly for 2 min. [19, 20]
Table 2: Typical Efavirenz loaded SNEDDS tablet composition

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Qty (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz loaded SNEDDS</td>
<td>100</td>
</tr>
<tr>
<td>MCC</td>
<td>200/300</td>
</tr>
<tr>
<td>PVP</td>
<td>12/20</td>
</tr>
<tr>
<td>SSG</td>
<td>8/16</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5</td>
</tr>
<tr>
<td>Talc</td>
<td>5</td>
</tr>
<tr>
<td>Lactose q.s</td>
<td>500</td>
</tr>
</tbody>
</table>

Evaluation of tablets [21, 22]

Hardness test

Monsanto hardness tester (Tab-Machines Ltd., India) was used to determine tablet hardness. Ten tablets were chosen randomly from the composite samples for each of the tableting runs and the average value was determined.

Disintegration test

The tablet disintegration test was performed employing disintegration tester (Disintegration Tester ED-2AL, Electrolab, Mumbai) using demineralized water at 37 ± 2°C. The time required for tablet disintegration was determined by visual observation. Each value reported is the maximum time of 6 independent measurements.

Friability

The friability of the tablets was determined by weighing 20 tablets dedusted prior testing in an analytical balance and moved for 4 min in an friability tester (Electrolab, EF2 Friabilator USP), set at speed of 25 revolutions per minute. After 4 min all loose dust was removed from the tablets, then they were reweighed and the percentage friability was calculated.

Drug content estimation

The drug was extracted from S SNEDDS using methanol, suitably diluted and analyzed using UV-VIS spectrophotometer (Shimadzu UV 1800, Japan) at a λmax of 247nm. The experimental studies were performed in triplicate.

Preparation of liquid SNEDDS

Efavirenz showed maximum solubility in Labrafac PG (Oil), tween 80 (Surfactant) and PEG 200 (Co surfactant) hence these excipients were selected for the preparation of SNEDDS. The characteristic peaks of efavirenz (3319 cm⁻¹, 1060 cm⁻¹, 750 cm⁻¹, 1039 cm⁻¹, 820 cm⁻¹) were not affected and prominently observed in IR spectra of efavirenz along with other excipients (figure not given). This clearly shows there is no interaction between drug and excipients.

Pseudo-ternary phase diagrams were constructed to identify the nanoemulsion regions and to optimize the concentration of the selected vehicles. The optimized formulation labrafac PG(15%) as oil, tween 80(19%) and PEG 200(38%) co surfactant was robust to all dilutions and did not show any phase separation or precipitation. The globule size of the formulation was found to be 142.7nm.

Preparation of S-SNEDDS

The oral pharmacokinetics of drug was assessed in Wistar rats (220-250 g) of either sex at a dose equivalent to 10 mg/kg of drug. Two types of systems were systematically compared: (i) drug-loaded S-SNEDDS, (ii) extemporaneous suspensions. In vivo study protocols were approved by the Institutional Animal Ethics Committee (Regd. No 107/2012). A wash out period of one month was given between testing of two products.

After collecting the zero hour blood sample (blank), the product in the study was administered orally with 10 ml of water. No food or liquid other than water was permitted until 4 hours following the administration of the product. Blood samples (0.5 ml) were collected from tail vein at 0.25, 0.5, 1, 2, 4, 8 and 12 hours after administration. The blood samples were collected in heparinized tubes and were centrifuged at 10000 rpm for 10 min and the plasma separated was collected into dry tubes. All the samples were stored under refrigerated conditions prior to assay on the same day. Plasma concentrations of drug were determined by a known HPLC method after revalidation [15].

Stability studies

The OPT S-SNEDDS formulation was subjected to stability studies, carried out at 40±2°C/70% ± 5% RH as per the ICH guidelines. The formulation was kept in air-tight glass vials and assayed periodically, at the time points of 0, 1, 3 and 6 months, for drug content and dissolution performance.

Results and Discussion

Preparation of liquid SNEDDS

Efavirenz showed maximum solubility in Labrafac PG (Oil), tween 80 (Surfactant) and PEG 200 (Co surfactant) hence these excipients were selected for the preparation of SNEDDS. The characteristic peaks of efavirenz (3319cm⁻¹, 1060cm⁻¹, 750 cm⁻¹, 1039 cm⁻¹, 820 cm⁻¹) were not affected and prominently observed in IR spectra of efavirenz along with other excipients (figure not given). This clearly shows there is no interaction between drug and excipients.

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Preparation of S-SNEDDS

The S-SNEDDS were prepared using carriers like aerosil, accurel and porous polystyrene beads. The mean particle size of aerosil was 12nm and has specific surface area (BET) 380±30 m²/g. Because of its small particle size and large specific surface area the S-SNEDDS prepared with aerosil had high loading efficiency and desirable flow characteristics (table 3). So it was selected as a suitable excipient for the preparation of S-SNEDDS.
The scanning electron micrographs of S-SNEDDS formulations were shown in fig. 1. The S-SNEDDS appeared as smooth-surfaced particles without any crystalline shape, indicating complete adsorption of SNEDDS. The SNEDDS prepared with aerosil appeared as rough-surfaced particles, indicating that the liquid SNEDDS was absorbed or coated inside the pores of silicon dioxide. The surface area of porous polystyrene beads and accurel also shows absence of crystalline particles indicating complete adsorption of SNEDDS.

**Differential Scanning Calorimetry**

The DSC thermograms of pure drug and S-SNEDDS were shown in fig. 2. The DSC thermograms showed pronounced melting peak for pure Efavirenz at 137.5°C correlating to its melting point. The absence of drug peak in S-SNEDDS was due to presence of drug in molecularly dissolved state in the vicinity of the lipid excipients. [14]. The SNEDDS loaded accurel shows melting at 152.25°C correlating to the melting point of accurel. PPB loaded SNEDDS shows melting peak at 82.05°C correlating to the melting point of PPB.

**Reconstitution properties of solid SEDDS**

The z-average diameter and polydispersity index of the solid and liquid SNEDDS are presented in Table 4. As shown, the z-average droplet sizes of both systems were less than 150 nm. The droplet size of the nanoemulsion from the solid SNEDDS was slightly increased, but the difference is not statistically significant compared to the liquid SNEDDS.

**Preparation of Efavirenz loaded SNEDDS tablet**

The experimental design methodology could be a very economic way to obtain maximum information, which can save a significant amount of time. Moreover, it can reduce the materials used for analyses and the personal costs as well. To identify the most important factors among all the factors screening is done at beginning of the experimental procedure. From the experimental results (Table 5), the effects of all studied variables and the variable interactions were graphically and statistically interpreted for all responses.
Table 5: Observed Response in $2^3$ Factorial Design for Efavirenz loaded SNEDDS tablet

<table>
<thead>
<tr>
<th>Std</th>
<th>Run</th>
<th>Factor 1 (A: MCC)</th>
<th>Factor 2 (B: PV)</th>
<th>Factor 3 (C: SSG)</th>
<th>Response 1 (Hardness)</th>
<th>Response 2 (Disintegration Time)</th>
<th>Response 3 (% Cumulative Drug Release)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>300.00</td>
<td>12.00</td>
<td>8.00</td>
<td>5.9</td>
<td>125</td>
<td>76.4</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>300.00</td>
<td>20.00</td>
<td>16.00</td>
<td>4.6</td>
<td>98</td>
<td>87.3</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>200.00</td>
<td>12.00</td>
<td>8.00</td>
<td>5.2</td>
<td>112</td>
<td>82.6</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>200.00</td>
<td>12.00</td>
<td>16.00</td>
<td>3.4</td>
<td>72</td>
<td>99.2</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>200.00</td>
<td>20.00</td>
<td>16.00</td>
<td>4.3</td>
<td>92</td>
<td>90.6</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>300.00</td>
<td>20.00</td>
<td>8.00</td>
<td>7.1</td>
<td>152</td>
<td>68.5</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>200.00</td>
<td>20.00</td>
<td>8.00</td>
<td>6.3</td>
<td>138</td>
<td>71.2</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>300.00</td>
<td>12.00</td>
<td>16.00</td>
<td>4</td>
<td>85</td>
<td>95.4</td>
</tr>
</tbody>
</table>

The results of ANOVA indicated that all models were significant ($p < 0.05$) for all response parameters investigated. Model simplification was carried out by eliminating non-significant terms ($p > 0.05$) in polynomial equations. Values of “Prob $> F$” less than 0.0500 in all the cases indicates model terms are significant. The Pred R-Squared is in reasonable agreement with the Adj R-Squared. The signal to noise ratio is measured by Adeq Precision and ratio greater than 4 is desirable. The value shows much higher than 4 confirms an adequate signal (Table 6).

Table 6: Summary of results of regression analysis for responses

<table>
<thead>
<tr>
<th>Response</th>
<th>Value</th>
<th>F-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R-Square</td>
<td>0.9865</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adj R-Squared</td>
<td>0.9763</td>
<td>97.16</td>
</tr>
<tr>
<td></td>
<td>Pred R-Squared</td>
<td>0.9458</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adeq Precision</td>
<td>26.291</td>
<td></td>
</tr>
<tr>
<td>Disintegration Time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R-Square</td>
<td>0.9867</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adj R-Squared</td>
<td>0.9768</td>
<td>99.08</td>
</tr>
<tr>
<td></td>
<td>Pred R-Squared</td>
<td>0.9469</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3 shows the effect plots for hardness, disintegration time, and friability, where negative values indicate a negative effect of a specific variable on the response factors. The application of factorial design yielded the following regression equations.

- **Hardness** = $+4.775+6.0E-003 \times MCC+0.118 \times PVP-0.256 \times SSG$
- **Disintegration Time** = $+105.0+0.115 \times MCC+2.68 \times PVP-5.62 \times SSG$
- **% Cumulative drug release** = $+84.22-0.04 \times MCC-1.12 \times PVP+2.30 \times SSG$

Hardness, Disintegration time and % Cumulative drug release values for all the eight formulations varied from 3.4 to 7.1 kg, 72-152s and 68.5-99.2% respectively. These outcomes depict that the variables chosen have strong influence on the selected responses.

Figure 3. Three-dimensional response surface plot depicting the impact of MCC:PVP, MCC:SSG and SSG:PVP on hardness, disintegration time and % drug release respectively

The MCC PH 101 having the particle size of 50μm that absorbs any squeezing of lipid occurs while punching of tablets. MCC has good wicking and absorbing capacities. PVP K 30 is used because of its directly compressible property that acts as binder. SSG acts
as super disintegrant. [MCC accelerates water penetration into tablets can cause easily swelling of SSG, and this reveals readily superdisintegrant property of SSG [22]. The excellent batch flowability and compressibility properties were attributed to the presence of microcrystalline cellulose, MCC, (Avicel 102), which is an excellent filler/flow-aid for direct compression. [24]

The figure 3. exhibits, as the concentration of PVP increases, the hardness of the tablets increases due to the increased bonding between the particles. Tablets of MCC disintegrated rapidly due to the rapid passage of water into the tablets resulting in the instantaneous rupture of the hydrogen bonds. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling by SSG. It was essential to use suitable inert compression diluents to improve the compactibility of tablets. In all the formulations, the hardness test indicated good mechanical strength and friability was less than 1%, which indicated that the tablets had a good mechanical resistance. The extent of dissolution, however, is dependent on the reversible attraction and surface adsorption of efavirenz and the oily formulation onto the adsorbents. Therefore, physical properties of the ingredients used to prepare the solid compacts have a profound effect on the emulsion release rate. This relationship between the formulation ingredients (independent variables) and emulsion release rates (dependent variables) was elucidated using 3 D graphs. [25]. Drug content was found to be 98-102% which was within the limits.

To optimize the final tablet formulation, the required limits of the response values were clearly defined, and the combinations of variables which resulted in tablets meeting the required specifications were calculated using the software to obtain tablets with the following properties: a hardness of 4, disintegration time of less than 80 sec and % cumulative release of more than 95%. To verify the reproducibility, a new formulation as shown in Table 7 was prepared according to the predicted levels and evaluated. The overlapping of the obtained result over the predicted values confirms the practicability and validation of the model.

<table>
<thead>
<tr>
<th>Number</th>
<th>MCC (mg)</th>
<th>PVP (mg)</th>
<th>SSG (mg)</th>
<th>Hardness (kg)</th>
<th>Disintegration Time (sec)</th>
<th>% Cumulative drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted</td>
<td>278.75</td>
<td>12.00</td>
<td>15.88</td>
<td>4</td>
<td>79.9</td>
<td>96.1</td>
</tr>
<tr>
<td>Actual</td>
<td>278.75</td>
<td>12.00</td>
<td>15.88</td>
<td>4</td>
<td>78</td>
<td>97</td>
</tr>
</tbody>
</table>

Pharmacokinetic studies

Plasma samples were analyzed for efavirenz employing reverse phase HPLC (RP-HPLC). The mobile phase consisted of acetonitrile:water (70:30). Each of the plasma samples was thawed to room temperature. One milliliter of diethyl-ether was added to it and mixed using a vortex mixer for 30 s. The upper organic phase was transferred and evaporated to dryness on a water bath at 50°C. To each dry residue, 0.5 ml of mobile phase was added, and mixed using the vortex mixer for 10 s to reconstitute the same. The reconstituted sample was transferred to the HPLC vials and injected into the integrated liquid chromatographic system Shimadzu LC-2010 HT equipped with a UV detector and a C18 column. The flow rate was kept at 1 ml min⁻¹ and the UV detector was set at an absorption max of 247 nm. From the chromatogram efavirenz was observed at retention time of 5.6 min [3, 26].

<table>
<thead>
<tr>
<th>Product</th>
<th>C_max (mcg/ml)</th>
<th>T_max (h)</th>
<th>K_d</th>
<th>T_1/2</th>
<th>(AUC)_0⁻t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>10.46</td>
<td>3.7</td>
<td>0.1776</td>
<td>3.9</td>
<td>95.39</td>
</tr>
<tr>
<td>Efavirenz S SNEDDS</td>
<td>42.6</td>
<td>1</td>
<td>0.2038</td>
<td>3.4</td>
<td>388.49</td>
</tr>
</tbody>
</table>

Table 8 shows significant improvement of drug absorption for the S SNEDDS than the pure drug. The results showed that Cmax of S SNEDDS was higher than that of pure drug. Additionally, Tmax of the S SNEDDS was all shorter than that of the pure drug, suggesting that SE technique could improve drug release and absorption in GIT. The relative bioavailability of the S SNEDDS and pure drug were 388.49% and 95.39%, respectively. It indicated that the absorption of efavirenz was evidently improved after it was dispersed in solid SE formulations as a dissolved state.

Stability studies

The optimized formulation was stable throughout the study period. There is no significant change in drug content and dissolution performance.

Conclusion

These current research evidenced the successful loading of efavirenz SNEDDS in aerosil by adsorption technique. Self emulsifying properties were still retained after loading and no significant changes in the particle size were observed. The S SNEDDS tablets were prepared by 2³ factorial design using design.
expert software. The results of ANOVA indicated that all models were significant. The model was used to predict the levels of the factors A, B and C required obtaining an optimum formulation with moderate hardness, minimum disintegration time and maximum % drug release. The observed values were in close agreement with the predicted values thereby validating the feasibility of the optimization procedure in developing self nanoemulsifying tablets. The in vivo study in wistar rats showed significantly enhanced bioavailability from S-SNEDDS compared with pure drug. Considering the significant increment of pharmacokinetic parameters (AUC and Cmax) and the thermodynamically and chemically stable drug delivery system, S SNEDDS may be an effective formulation strategy for the other BCS class II and IV drugs.

Authors’ contributions
PS designed the work under the guidance of PKK. All the work starting from designing the experiment, performing, interpreting was done PS. PKK involved in the analyzing the data’s and carrying out analytical work. PS drafted the article with the suggestion of PKK.

Conflicts of interest
Authors have no conflicts of interest.

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References


