

Development and *In Vitro* Characterization of Neusilin® US2-Based Solid Self-Nanoemulsifying Drug Delivery System for Oral Administration of Finasteride

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Development and In Vitro Characterization of Neusilin® US2-Based Solid Self-Nanoemulsifying Drug Delivery System for Oral Administration of Finasteride

Finasteridin Oral Uygulanması için Neusilin® US2 Temelli Katı Kendiliğinden Nanoemülsifiye İlaç Taşıyıcı Sisteminin Geliştirilmesi ve İn Vitro Karakterizasyonu

SUMMARY

In this study, we aimed to develop a Neusilin® US2-based solid self-nanoemulsifying drug delivery system (S-SNEDDS) for the oral administration of finasteride (FNS), a poorly water-soluble drug classified as BCS Class II. Formulation studies resulted in an optimized SNEDDS composed of Labrafil®, Cremophor® EL, and Tween® 20. This formulation exhibited a small droplet size, low polydispersity index, rapid self-nanoemulsification, and high thermodynamic stability. The SNEDDS was converted into a solid dosage form by adsorption onto Neusilin® US2, a highly porous carrier with a large specific surface area, and different SNEDDS-to-carrier ratios (1:1, 1.5:1, and 2:1) were evaluated. The S-SNEDDS formulation prepared at a 2:1 ratio was identified as the optimal composition due to its acceptable flow properties and high liquid-loading capacity. Solid-state analyses using DSC, XRPD, FTIR, and SEM demonstrated that FNS lost its crystalline structure and was present in an amorphous or molecularly dispersed state within the solid system, without evidence of chemical interaction with the excipients. The developed S-SNEDDS capsules met European Pharmacopoeia 11.0 for content uniformity, mass variation, and disintegration tests. In vitro dissolution studies conducted in pH 7.4 phosphate buffer containing 0.5% sodium lauryl sulfate and in biorelevant media indicated that, despite a controlled release in the early phase, complete drug dissolution comparable to the reference product (Propecia® tablets) was achieved at later time points. In conclusion, the Neusilin® US2-based S-SNEDDS capsules developed represent a promising solid oral dosage form for FNS, offering improved stability, effective drug delivery, and the potential to enhance patient adherence.

Keywords: Finasteride, alopecia, Neusilin® US2, solid self-nanoemulsifying drug delivery systems (S-SNEDDS).

ÖZ

Bu çalışmada, düşük suda çözünürlüğe sahip BCS Sınıf II bir etkin madde olan finasteridin (FNS) oral uygulanmasına yönelik olarak Neusilin® US2 temelli katı kendiliğinden nanoemülsifiye ilaç taşıyıcı sistemi (S-SNEDDS) geliştirilmiş ve kapsamlı şekilde karakterize edilmiştir. Formülasyon çalışmaları sonucunda Labrafil®, Cremophor® EL ve Tween® 20 içeren optimize bir SNEDDS formülasyonu elde edilmiştir. Bu formülasyonun küçük damlacık boyutu, düşük polidispersite indeksi, bızlı kendiliğinden emülsifikasyon süresi ve yüksek termodinamik stabilite sergilediği belirlenmiştir. SNEDDS, yüksek yüzey alanı ve gözenekliliğe sahip Neusilin® US2 üzerine adsorpsiyon yöntemiyle katılaştırılmış ve farklı SNEDDS: taşıyıcı oranları (1:1, 1,5:1, 2:1) değerlendirilmiştir. 2:1 oranında hazırlanan S-SNEDDS formülasyonu, kabul edilebilir akış özellikleri ve yüksek sıvı yükleme kapasitesi ile optimum kompozisyon olarak belirlenmiştir. DSC, XRPD, FTIR ve SEM analizleri, FNS'nin katı sistem içerisinde kristal yapısını kaybederek amorf veya moleküler dağılmış halde bulunduğunu ve yardımcı maddelerle kimyasal etkileşime girmediğini ortaya koymuştur. Geliştirilen S-SNEDDS kapsülleri Avrupa Farmakopesi 11.0 gerekliliklerini karşılamış; içerik homojenliği, ağırlık sapması ve dağılıma testlerinde uygun sonuçlar elde edilmiştir. %0,5 sodyum lauril sülfat içeren pH 7,4 fosfat tamponu ve biyoyoumlu çözünme ortamında yapılan in vitro çalışmalar, erken fazda kontrollü bir salım gözlenmesine rağmen, ileri zaman noktalarında referans ürünle (Propecia® tablet) karşılaştırılabilir düzeyde tam çözünmenin sağlandığını göstermiştir. Sonuç olarak, geliştirilen Neusilin® US2 temelli S-SNEDDS kapsüller, FNS'nin oral verilmesi için stabil, etkin ve hasta uyuncunu artırabilecek umut verici bir katı dozaj formu olarak değerlendirilmiştir.

Anahtar Kelimeler: Finasterid, alopesi, Neusilin® US2, katı kendiliğinden nanoemülsifiye ilaç taşıyıcı sistemler (S-SNEDDS).

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INTRODUCTION

Androgenetic alopecia (AGA) is a common, progressive form of hair loss that is associated with aging, genetic predisposition, and elevated androgen levels (Lis-Świąty et al., 2018). It is also referred to as male-pattern hair loss (Lolli et al., 2017). It is the most prevalent cause of hair loss, affecting approximately 40% of women and 85% of men worldwide (Phillips et al., 2017). Hair loss may arise from multiple factors, including hormonal imbalance, genetic susceptibility, and systemic diseases. Although a certain degree of daily hair shedding is considered physiological, the loss of more than 100 hairs per day is generally regarded as indicative of a pathological condition (Sadgrove et al., 2023). The hair growth cycle consists of four distinct phases: anagen, catagen, telogen, and exogen. In AGA, successive anagen cycles progressively shorten, and the reduced anagen duration leads to gradual miniaturization of genetically predisposed hair follicles in the presence of androgens (Rambawasvika et al., 2021).

Dihydrotestosterone (DHT) is a potent androgen produced by the type II 5- α -reductase-mediated metabolism of testosterone (Devjani et al., 2023). The binding of DHT to androgen receptors in hair follicles results in progressive follicular miniaturization, weakening, and eventual follicle destruction. Consequently, 5- α -reductase inhibitors are widely employed to reduce hair loss, prevent follicular deterioration, or stabilize newly growing hair (Kim et al., 2019). Finasteride (FNS) is a synthetic antiandrogen used in the treatment of AGA by inhibiting the conversion of testosterone to DHT (Santana et al., 2023). Orally administered FNS is approved exclusively for use in men and is contraindicated in women who are pregnant or may become pregnant due to the risk of teratogenicity in male fetuses (FDA, 2010). Nevertheless, owing to its proven efficacy in AGA, it has been hypothesized that 5- α -reductase inhibition with FNS may also provide therapeutic benefit in female pattern hair loss (Stout & Stumpf, 2010).

FNS is classified as a Biopharmaceutics Classification System (BCS) Class II drug, characterized by low aqueous solubility and high permeability. It exhibits very low water solubility (0.05 mg/mL) and is considered practically insoluble in water. Following oral administration, approximately 65% of the dose is absorbed from the gastrointestinal tract (FDA, 2010). Currently, FNS is commercially available for the treatment of AGA as an oral tablet formulation (Propecia® 1 mg film-coated tablet, reference product), with a recommended daily dose of 1 mg taken with or without food. However, systemic adverse effects associated with oral FNS therapy, including teratogenicity, decreased libido, erectile dysfunction, and ejaculatory disorders, represent major limitations to long-term treatment adherence.

Reducing systemic adverse effects associated with oral FNS administration while improving patient compliance is crucial in the management of AGA, particularly to prevent emotional distress and psychological complications that negatively impact quality of life (Huang et al., 2021). Accordingly, the primary objective of the present study was to enhance the solubility and *in vitro* dissolution rate of FNS, thereby enabling dose reduction through the development of self-nanoemulsifying drug delivery systems (SNEDDS). SNEDDS are isotropic mixtures composed of oils, surfactants, and cosurfactants that spontaneously form oil-in-water nanoemulsions under gastrointestinal conditions, even in the presence of minimal aqueous phase and physiological motility (Usta et al., 2022). Although SNEDDS are frequently utilized to improve the solubility and dissolution behavior of poorly water-soluble, lipophilic drugs, they present several limitations, including low physical stability, leakage of oily components during packaging and transportation, gastrointestinal irritation due to high surfactant content, and the high cost and operational complexity of soft gelatin capsule filling equipment. Solid self-nanoemulsifying drug delivery systems (S-SNEDDS) have emerged as an effective al-

ternative strategy, combining the enhanced solubility and bioavailability benefits of SNEDDS with the inherent advantages of solid dosage forms, such as lower production costs, ease of process control, improved stability and reproducibility, and enhanced patient compliance (Usta et al., 2025; Usta & Teksin, 2025a).

Furthermore, due to their superior stability and convenience in handling and transportation, S-SNEDDS are generally preferred over liquid SNEDDS. Solid carriers can adsorb liquid or semi-solid self-emulsifying systems. Several techniques are available for preparing S-SNEDDS, including adsorption onto solid carriers, spray drying, dry emulsion, solid dispersion, and melt extrusion. Afterward, the resulting systems can be converted into pellets, tablets, or capsules (Tanga et al., 2026). In the present study, the adsorption method was selected for its simplicity and cost-effectiveness, followed by the encapsulation of the resulting S-SNEDDS. This method yields a freely flowing powder through a simple mixing process, which can subsequently be formulated with appropriate excipients into solid dosage forms with good content uniformity (Smitha et al., 2025).

Neusilin® US2 is a synthetic, amorphous form of magnesium aluminometasilicate ($\text{Al}_2\text{O}_3 \cdot \text{MgO} \cdot 1.7\text{SiO}_2 \cdot x\text{H}_2\text{O}$) characterized by a large specific surface area, high porosity, and superior oil adsorption capacity (Kostelanská et al., 2022). It has been widely accepted that pharmaceutical formulations containing antibiotics, lipophilic and poorly soluble active ingredients, herbal preparations, and vitamins are suitable for this approach (Usta et al., 2023). In pharmaceutical applications, Neusilin® US2 is extensively used as a carrier and filler to improve the quality of tablets, powders, granules, and capsules, as well as a solid carrier for solid dispersions and SNEDDS.

To the best of our knowledge, no studies to date have reported the development and characterization of Neusilin® US2-based S-SNEDDS solid dosage forms containing FNS, rendering the present

work both original and innovative. The design of a lipid-based oral solid dosage form of FNS is expected to provide significant advantages over currently marketed formulations by enhancing solubility and dissolution rate, thereby enabling dose reduction and minimizing systemic adverse effects. The findings of this study are anticipated to make a meaningful contribution to existing literature.

MATERIALS AND METHODS

Materials

FNS was purchased from Sigma-Aldrich (Germany). Sodium lauryl sulfate (SLS), Tween® 80, Tween® 20, tri-sodium phosphate dodecahydrate, and hydrochloric acid (HCl) were purchased from Merck (Germany). Cremophor® RH40 was purchased from BASF (Germany). Cremophor® EL was provided as a gift sample by BASF (Türkiye). Capmul® MCM C8 was provided as a gift sample by Abitec (USA). Labrafil® M 2125 CS, Capryol® 90, Maisine®, and Labrasol® were provided as gift samples by Gattefossé (France). Neusilin® US2 was purchased from Fuji Chemical Industries (Japan). The FaSSIF-V2 (biorelevant media) was purchased from Biorelevant (United Kingdom). All the other chemicals and reagents used were of analytical grade.

Method for quantification of FNS

The quantitative analysis of FNS was performed using a validated HPLC method (Agilent 1220 Infinity LC, Germany). The chromatographic separation was performed using the XSelect® C 18 (5 µm, 4.6 x 250 mm) (Waters, Ireland). The separation was achieved using a 60:40 (v/v) acetonitrile: water solution. The flow rate was 1.0 mL/min, and the injection volume was 100 µL. The detector wavelength was set at 254 nm for determination. A stock solution of FNS (100 µg/mL) was prepared containing 0.5% SLS in pH 7.4 phosphate buffer saline (PBS). Working standard solutions ranging from 0.1 to 25 µg/mL were obtained by appropriate serial dilutions of the stock solution with the same buffer. The FNS amount was calculated from the peak area. The method was further validated

ed for precision, accuracy, and reproducibility in accordance with ICH Q2(R2) guidelines (ICH Q2(R2), 2023).

Pseudo-ternary phase diagram, preparation, and characterization of SNEDDS

Various oil-to-surfactant/co-surfactant ratios (1:9 to 9:1) were used to determine the optimal surfactant:co-surfactant ratio (S_{mix}). The pseudo-ternary phase diagrams were created by titration with water. The pseudo-ternary phase diagrams were constructed by identifying the self-nanoemulsifying region using the phase diagram program (Usta & Teksin, 2025b).

Different ratios of lipid, surfactant, and co-surfactant were used to create a series of pre-formulations. The ingredients were precisely weighed and combined at 40 °C to create a uniform, isotropic mixture, which was then stored at room temperature in tightly sealed glass vials. Self-nanoemulsifying systems were prepared by mixing of oil phase; Capryol® 90, Maisine®, Labrafil® M 2125 CS, and Capmul® MCM, surfactant; Tween® 80, Cremophor® RH40, and Cremophor® EL, co-surfactant; Labrasol® and Tween® 20. Oil and surfactant:co-surfactant ratios were blended for each sample in ratios ranging from %10:90 to %90:10. Following the identification of the self-emulsifying region, the appropriate SNEDDS (for Type IIIB formulations) component ratios were chosen according to the lipid formulation classification system (LFCS) (Usta & Teksin, 2025b). The optimum formulation was determined by evaluating the polydispersity index (PDI), droplet size, and emulsification efficiency. FNS was added to the optimum blank SNEDDS for drug loading. For the optimum FNS-loaded SNEDDS formulation, the ingredients were vortexed until a homogeneous mixture was obtained. The final formulation was then stirred at 37 °C with a magnetic stirrer. SNEDDS was stored at 25 °C until use.

Droplet size and PDI measurements were performed using a Malvern Zetasizer (Nano ZS, Malvern Instruments, UK). Nanoemulsions were prepared by dispersing 1 mL of the formulation into 250 mL of

the appropriate medium at 25 ± 0.5 °C before analysis.

The self-nanoemulsification behavior of SNEDDS formulations was evaluated through a spontaneous emulsification test, which involved visual inspection for any evidence of drug precipitation or phase separation upon dilution with an aqueous phase (Zafar et al., 2022). Dispersibility and self-emulsification times were studied to assess the efficiency of self-nanoemulsification. For this purpose, 1 mL of each formulation was introduced into 500 mL of distilled water maintained at 37 ± 0.5 °C and gently agitated at 50 rpm. The *in vitro* performance of the formulations was assessed using a visual grading system (Beg et al., 2013). In addition, the time required for the form of a clear and uniform nanoemulsion was recorded by adding 1 mL of the formulation to 250 mL of distilled water at 37 °C under continuous magnetic stirring at 50 rpm.

The optical clarity of both blank and FNS-loaded SNEDDS formulations was assessed using a UV-visible spectrophotometer. Distilled water was employed as the reference, and percent transmittance was measured at 650 nm. Formulations exhibiting transmittance values exceeding 99% were considered optically transparent (Timur et al., 2026). The influence of dilution ratio and medium pH on droplet size and PDI was investigated by diluting the formulations at ratios of 1:50 and 1:200 in enzyme-free pH 6.8 buffer and distilled water.

Thermodynamic stability studies were conducted to evaluate the physical robustness of SNEDDS formulations with and without FNS. Heating-cooling cycles were applied between 4 °C and 45 °C, with each temperature maintained for at least of 48 hours across three consecutive cycles. Following this process, formulations were centrifuged at 3500 rpm for 30 minutes to detect any signs of phase separation. Formulations that remained homogeneous were subsequently subjected to freeze-thaw cycles consisting of three 48-hour periods alternating between -2 °C and 25 °C (Timur et al., 2022). After completion of these stability assessments, the formulations were diluted with

distilled water at a 1:250 ratio and examined for precipitation, phase separation, and changes in droplet size or PDI.

The morphology of nanoemulsion droplets was examined using transmission electron microscopy (TEM) (FEI Tecnai G2 Spirit Biotwin, USA). Samples diluted 1:250 with distilled water were placed on copper grids and negatively stained with 1% (w/v) phosphotungstic acid. After allowing the samples to stand for 5 minutes at 25 °C, excess liquid was removed using filter paper. The grids were air-dried at room temperature and analyzed at an accelerating voltage of 120 kV (Yilmaz Usta & Teksin, 2024).

Long-term physical stability of blank and FNS-loaded SNEDDS formulations was evaluated at 0, 1, 3, and 6 months by monitoring droplet size, PDI, and visual appearance. Stability studies were performed under refrigerated conditions (4 °C), room temperature (25 ± 2 °C / 60 ± 5% relative humidity-RH), and accelerated conditions (40 ± 2 °C / 75 ± 5% RH) in accordance with ICH stability guidelines.

Preparation and solid-state characterization of S-SNEDDS

The FNS-loaded SNEDDS was solidified through adsorption onto Neusilin® US2 to obtain S-SNEDDS. Solid formulations were prepared at liquid-to-carrier weight ratios of 1:1, 1.5:1, and 2:1. The liquid formulation was gradually incorporated into the adsorbent and gently blended in a mortar until a uniform, free-flowing powder was achieved. The prepared S-SNEDDS powders were then stored in a desiccator under dry conditions until further characterization and evaluation.

The flow properties of FNS-loaded S-SNEDDS prepared at liquid SNEDDS to carrier ratios of 1:1, 1.5:1, and 2:1 were evaluated in accordance with European Pharmacopoeia (EP 11.0) (Section 2.9.34. Bulk density and tapped density of powders and 2.9.36 Powder flow).

Bulk density was measured by gently transferring accurately weighed powder samples into a 100 mL graduated cylinder with a readable scale of 1 mL. The untapped volume was recorded, after which the cylinder was tapped at a drop height of 2.5 cm with 2-second intervals until a constant volume was obtained. Bulk and tapped densities were calculated using Eq. 1 and Eq. 2, respectively:

$$\text{Bulk density } (\rho_b) = \text{Mass of powder sample (g)} / \text{Bulk volume (mL)} \quad (1)$$

$$\text{Tapped density } (\rho_t) = \text{Mass of powder sample (g)} / \text{Tapped volume (mL)} \quad (2)$$

Hausner's ratio (HR), an indicator of powder flow behavior, is calculated as the ratio of tapped density to bulk density (Ali & Hussein, 2017). This parameter reflects interparticulate friction and cohesion; lower values indicate improved flowability. HR values typically range from approximately 1.2 for free-flowing powders to about 1.6 for highly cohesive materials. HR was evaluated in accordance with EP 11.0 (Eq. 3).

$$\text{HR} = \rho_t / \rho_b \quad (3)$$

The angle of repose of the S-SNEDDS powders was determined using the fixed funnel method. The height (h) and radius (r) of the formed powder cone were measured, and the angle of repose (θ) was calculated using Eq. 4. The obtained values were interpreted based on EP 11.0 criteria for powder flow characteristics.

$$\tan \theta = h / r \quad (4)$$

The molecular and physical state of FNS within the S-SNEDDS matrix was investigated. The thermal behavior of pure FNS, blank, and FNS-loaded S-SNEDDS (1:1, 1.5:1, and 2:1) was analyzed using differential scanning calorimetry (DSC-60, Shimadzu Scientific Instruments, Japan). Approximately 2 mg of each sample was sealed in aluminum pans and heated from 20 °C to 300 °C at a constant rate of 10°C/min. The resulting thermograms were evaluated for melting transitions, peak maxima, shifts in endothermic events, and the emergence of additional thermal features.

Crystalline characteristics of FNS, Neusilin® US2, blank, and FNS-loaded S-SNEDDS (1:1, 1.5:1, and 2:1) were assessed by X-ray powder diffraction (XRPD) using a Rigaku Ultima IV diffractometer (Germany) operated at 40 kV and 30 mA. Diffraction patterns were collected over a 2θ range of 2° to 60° with a step size of 0.02° , allowing evaluation of changes in crystallinity and solid-state transformation.

Fourier transform infrared (FTIR) spectroscopy was employed to investigate potential molecular interactions between FNS and formulation excipients. Spectral data for the pure drug, individual excipients, blank SNEDDS, and FNS-loaded SNEDDS were recorded using an FTIR spectrophotometer (Spectrum 400, PerkinElmer, USA) over the range of $4000\text{--}650\text{ cm}^{-1}$.

Surface morphology and particle characteristics of pure FNS, Neusilin® US2, blank, and FNS-loaded S-SNEDDS (1:1, 1.5:1, and 2:1) were examined by scanning electron microscopy (SEM) (Quanta FEG 400, FEI, USA). Samples were sputter-coated with a gold–palladium layer before imaging and were acquired at an accelerating voltage of 30 kV under different magnification levels.

Preparation and characterization of FNS-loaded S-SNEDDS capsules

The FNS-loaded SNEDDS formulations were prepared by homogeneously blending the liquid SNEDDS with Neusilin® US2 at weight ratios of 1:1, 1.5:1, and 2:1 using a mortar. Based on preliminary characterization studies, the formulation exhibiting optimal physicochemical properties was selected, and the resulting S-SNEDDS powder was filled into size 00el hard gelatin capsules (Capsugel®, Belgium). Following capsule filling, a series of quality control tests was conducted in accordance with EP 11.0 to demonstrate batch uniformity, ensure consistent product performance, and confirm the reproducibility of the manufacturing process.

The uniformity of content test was performed to verify that the FNS content in individual capsules

complied with the specified limits defined in EP 11.0 (Section 2.9.6). The individual contents of the active substance(s) in 10 dosage units, taken at random, were accurately weighed and analyzed using a validated HPLC method. The results were expressed as mean value and standard deviation (SD). Acceptance criteria were defined as 85–115% of the declared content, in accordance with EP requirements for solid oral dosage forms.

Uniformity of mass was evaluated in compliance with EP 11.0 (Section 2.9.5). Initially, 10 filled capsules were weighed collectively to determine the mean capsule mass, after which each capsule was weighed individually. Each mass was required to fall within 90–110% of the calculated mean value. According to EP acceptance criteria, no more than two capsules were permitted to deviate by more than $\pm 10\%$ from the mean mass, and no capsule was allowed to deviate by more than $\pm 25\%$.

The disintegration test was carried out in accordance with EP 11.0 (Section 2.9.1). The test was performed using simulated gastric fluid (pH 1.2, HCl) as the disintegration medium. Capsules were placed in the disintegration test apparatus, and the basket assembly was operated in the medium maintained at $37 \pm 0.5^\circ\text{C}$. The repeated immersion and withdrawal of the capsules facilitated disintegration, which was visually monitored. Complete disintegration of the capsules was expected within 15–30 minutes, in line with pharmacopoeia specifications.

A reconstitution study was conducted to confirm that the solidification of the liquid SNEDDS did not adversely influence the droplet size characteristics of the resulting nanoemulsion. For this purpose, the S-SNEDDS capsules were dispersed in 250 mL of purified water and magnetically stirred at 25°C for 1 hour. Following dispersion, the undissolved solid fraction was removed by filtration through a $0.45\text{ }\mu\text{m}$ membrane filter. Droplet size and PDI of the nanoemulsion generated from the S-SNEDDS capsules were subsequently determined at $25 \pm 0.5^\circ\text{C}$ using a Malvern Zetasizer.

The physical and chemical stability of FNS-loaded S-SNEDDS capsules was assessed under various storage conditions, including refrigerated ($4\text{ }^{\circ}\text{C}$), long-term ($25 \pm 2\text{ }^{\circ}\text{C}$ / $60 \pm 5\%$ RH), and accelerated ($40 \pm 2\text{ }^{\circ}\text{C}$ / $75 \pm 5\%$ RH) conditions. Stability evaluations were performed at predetermined intervals (0, 1, 3, and 6 months), during which drug content and physical appearance of the capsules were systematically examined.

***In vitro* dissolution studies**

In vitro dissolution studies on FNS-loaded S-SNEDDS capsules were carried out using the USP Apparatus II (Agilent Technologies, 708-DS, US) using 900 mL 0.5% containing SLS in pH 7.4 PBS and FaSSIF-V2 at $37 \pm 0.5\text{ }^{\circ}\text{C}$ at a rotation speed of 50 rpm. For comparison with the formulation, the FNS powder, FNS-loaded SNEDDS, and Propecia® tablets were used. Aliquots of 5 mL were withdrawn at predetermined time points (5, 10, 15, 20, 30, 45, 60, 90, and 120 minutes), and the sampled volume was immediately replaced with fresh dissolution medium to maintain sink conditions. The amount of FNS released was quantified by a validated HPLC method, and cumulative drug release was calculated as a percentage. All dissolution experiments were carried out in triplicate.

Statistical analysis

Student's t-test was used for statistical analysis of data when comparing two groups, and one-way analysis of variance (ANOVA) was used for comparisons of multiple groups. A significant difference between groups was determined when $p < 0.05$. When groups were homogeneous, the Tukey HSD post hoc test was used to determine which groups differed.

RESULTS and DISCUSSION

HPLC method for quantification of FNS

The regression analysis showed good linearity within the specified concentration range, with a correlation coefficient (R^2) greater than 0.999, confirming the suitability of the method for quantitative analysis for 0.5% containing SLS in pH 7.4 PBS and FaSSIF-V2. The intra- and inter-day precision results exhibited relative standard deviations (RSD) of less than 2%, while recovery studies indicated accuracies of 101–102%. These findings demonstrate that the proposed HPLC method is simple, sensitive, and reliable for the routine quantification of FNS studies. The detailed validation data are not shown in the manuscript but can be provided upon request.

Pseudo-ternary phase diagram, preparation, and characterization of SNEDDS

The solubility of FNS in various oils, surfactants, and co-surfactants was identified based on a comprehensive literature search for the scope of SNEDDS development (Ahmed et al., 2018; Fagir et al., 2015; Irfan et al., 2021; Mohammad Soleymani & Salimi, 2019; Rehman et al., 2022; Subongkot et al., 2022). Pseudo-ternary phase diagrams were constructed by water titration using different combinations of oils, surfactants, and co-surfactants. Selected surfactant and co-surfactant mixtures (S_{mix}) were prepared at two different weight ratios (9:1 and 4:1). Each S_{mix} was combined with the selected oil at nine different ratios, resulting in a total of 45 mixtures. Based on this data, pseudo-ternary phase diagrams were generated to identify the self-nanoemulsifying regions. From the constructed phase diagrams, the most suitable compositions and concentration ranges were selected, and five optimal SNEDDS formulations were identified. The corresponding pseudo-ternary phase diagrams are presented in Figure 1. These formulations were further evaluated in terms of droplet size, PDI, self-nanoemulsification time, dispersibility, and viscosity (Table 1.).

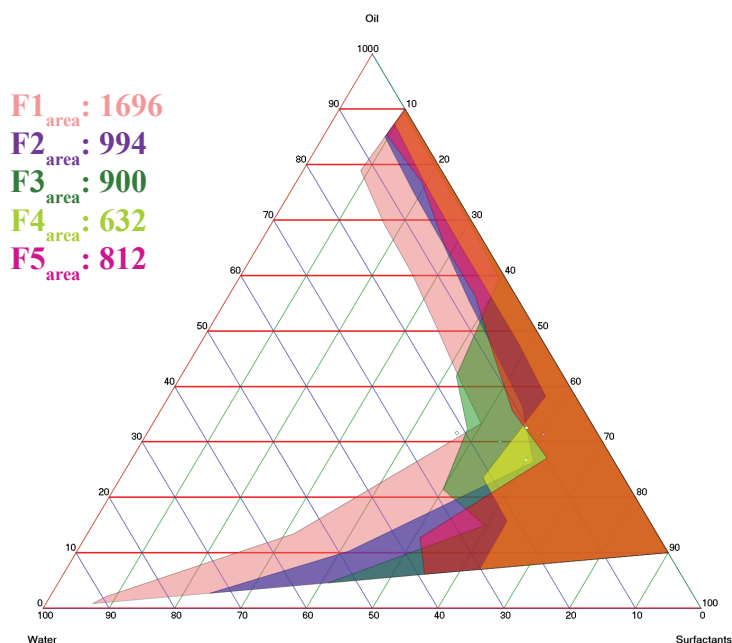


Figure 1. Pseudo-ternary phase diagrams of formulations

Table 1. Characterization results of formulation studies

	S_{mix}	SNEDDS composition (%w/w)			DS* (nm)	PDI*	ST (sec)	D	V (cP)
		Oil	Surfactant	Co-surfactant					
F1	9:1	Capryol® 90 15.0	Cremophor® RH40 76.5	Labrasol® 8.50	15.1±0.78	0.251±0.030	27	Grade A	416
F2	4:1	Capryol® 90 15.0	Tween® 80 68.0	Labrasol® 17.0	21.9±0.33	0.578±0.017	25	Grade A	236
F3	4:1	Labrafil® 15.0	Cremophor® EL 68.0	Tween® 20 17.0	16.1±0.87	0.181±0.013	38	Grade A	590
F4	4:1	Maisine® 15.0	Cremophor® EL 68.0	Tween® 20 17.0	166±14.9	0.823±0.051	283	Grade B	573
F5	9:1	Capmul® 15.0	Cremophor® RH40 76.5	Labrasol® 8.50	15.8±0.88	0.244±0.021	30	Grade A	544

S_{mix} : Surfactant: co-surfactant ratio, **DS**: Droplet size, **PDI**: Polydispersity index, **ST**: Self-nanoemulsification time, **D**: Dispersibility, **V**: Viscosity, *n=3, mean ± standard deviation (SD)

Upon oral administration, SNEDDS formulations are expected to rapidly and completely disperse in the gastrointestinal lumen under mild agitation caused by peristaltic movements, forming nanoemulsions upon contact with GI fluids (Balakumar et al., 2013). The resulting nanoemulsions must remain physically stable upon dilution, without phase separation or drug precipitation, particularly for poorly water-soluble drugs that are prone to phase transitions (Shakeel et al., 2014). The dispersibility behavior of F1, F2, F3,

and F5 SNEDDS formulations was classified as Grade A, indicating rapid nanoemulsion formation within 1 minute, accompanied by a clear or slightly bluish appearance (Table 1.). Grade A formulations were shown to form stable nanoemulsions under gastrointestinal conditions (Parmar et al., 2011). Grade B indicates the formation of a slightly less clear nanoemulsion with a bluish-white appearance and a slower (generally within 2 minutes) emulsification process compared with Grade A systems. Self-emulsification efficiency can

also be assessed by the time required to form a transparent nanoemulsion, with emulsification rate being a critical performance parameter. Ideally, SNEDDS formulations should disperse rapidly and completely upon aqueous dilution without drug precipitation (Prajapat et al., 2017). In this study, F1, F2, F3, and F5 formulations exhibited self-emulsification times of less than 1 minute and formed transparent systems within this time (Table 1.).

Droplet size is a critical determinant of *in vivo* drug release rate and extent, as smaller droplets provide a larger interfacial surface area, thereby enhancing dissolution and bioavailability of poorly soluble drugs (Kassem et al., 2016). The oil-surfactant mixture contacts water, forming an interfacial region between the oil and aqueous phases. Penetration of the surfactant into this interface disrupts the interfacial tension, leading to the spontaneous formation of fine droplets. Improved self-emulsification performance is associated with smaller droplet sizes. The SNEDDS systems are generally reported to exhibit droplet sizes within the range of 10–200 nm, depending on formulation composition and measurement conditions (Tanga et al., 2026). In the present study, all formulations produced nanoemulsions with droplet sizes between 10 and 200 nm (Table 1.).

The PDI, defined as the ratio of the standard deviation to the mean droplet size, reflects the uniformity of droplet size distribution within a formulation (Da-

naei et al., 2018). Lower PDI values indicate a more homogeneous droplet population, whereas higher values signify increased heterogeneity. PDI values below 0.3 are generally considered acceptable for SNEDDS formulations, while values below 0.2 indicate a more uniform droplet size distribution (Tungadi, 2024). Although formulation F2 showed relatively low variation in droplet size measurements, its high PDI value (0.578) indicated a heterogeneous droplet size distribution. Therefore, this formulation was not considered suitable for further optimization. In this study, F1, F3, and F5 formulations exhibited PDI values below 0.3 (Table 1.).

Based on the overall characterization results, formulation F3 was identified as the optimal SNEDDS formulation. F3 exhibited a small droplet size (16.1 nm), low PDI (<0.2), rapid self-nanoemulsification time (<1 minute), and Grade A dispersibility (Table 1.), indicating efficient nanoemulsion formation and a homogeneous droplet distribution. In conclusion, drug-loading studies were performed using the F3 formulation, and all subsequent characterization studies were carried out on both the blank F3 SNEDDS (without FNS) and the FNS-loaded SNEDDS formulation. As a result of the formulation studies, 2.48 mg of FNS was incorporated into 1 g of the optimized SNEDDS formulation comprising 16.2% Labrafil®, 64.5% Cremophor® EL, and 19.3% Tween® 20. The characterization studies are summarized in Table 2 for blank and FNS-loaded SNEDDS.

Table 2. Characterization studies of blank and FNS-loaded SNEDDS

	DS (nm)*	PDI*	ST (sec)	D	T (%)*	Viscosity (cP)
Blank SNEDDS	16.1 ± 0.87	0.181 ± 0.013	54	Grade A	99.3 ± 0.023	590
FNS-loaded SNEDDS	15.9 ± 0.55	0.194 ± 0.041	92	Grade A	99.6 ± 0.032	624

DS: Droplet size, PDI: Polydispersity index, ST: Self-nanoemulsification time, D: Dispersibility, T: Transmittance, *n=3, mean ± SD

High transmittance values indicate the formation of a transparent system with small droplets and minimal light scattering. A formulation is considered optically transparent when the transmittance exceeds 99% (Table 2.).

Ensuring consistent nanoemulsion formation under varying dilution conditions is essential for SNEDDS performance, as the volume and pH of gastrointestinal fluids vary among individuals. Investigating the impact of dilution ratio and medium pH

on emulsion formation and drug precipitation under *in vitro* conditions provides insight into *in vivo* performance (Balakumar et al., 2013). Accordingly, the effects of different dilution media and ratios were evaluated using distilled water and pH 6.8 phosphate

buffer, diluted 50- and 200-fold to simulate intestinal conditions. The formulations were assessed based on visual appearance, droplet size, and PDI. The results are summarized in Table 3, and no significant change was observed ($p>0.05$).

Table 3. Results of pH and robustness to dilution for blank and FNS-loaded SNEDDS

	Dilution ratio	Droplet size (nm)		PDI	
		Blank SNEDDS	FNS-loaded SNEDDS	Blank SNEDDS	FNS-loaded SNEDDS
Distilled water	1:50	14.3 ± 0.82	13.7 ± 0.63	0.146 ± 0.011	0.105 ± 0.015
	1:200	14.5 ± 0.58	15.7 ± 0.41	0.180 ± 0.024	0.200 ± 0.008
pH 6.8	1:50	15.6 ± 0.32	15.5 ± 0.75	0.113 ± 0.027	0.139 ± 0.016
	1:200	19.1 ± 2.62	18.6 ± 0.37	0.229 ± 0.014	0.258 ± 0.016

n=3, mean ± SD

Thermodynamic stability studies were conducted to evaluate the formulations' resistance to stress conditions, including temperature fluctuations and mechanical stress, without phase separation or drug precipitation (Kallakunta et al., 2012). Heating-cooling cycles, centrifugation, and freeze-thaw tests revealed no signs of precipitation or phase separation. Initially,

the thermodynamic stability of blank SNEDDS formulations was confirmed, followed by the evaluation of FNS-loaded SNEDDS. After dilution with distilled water (1:250), droplet size and PDI values were measured, and no statistically significant differences were observed before and after thermodynamic stability studies ($p>0.05$) (Figure 2.).

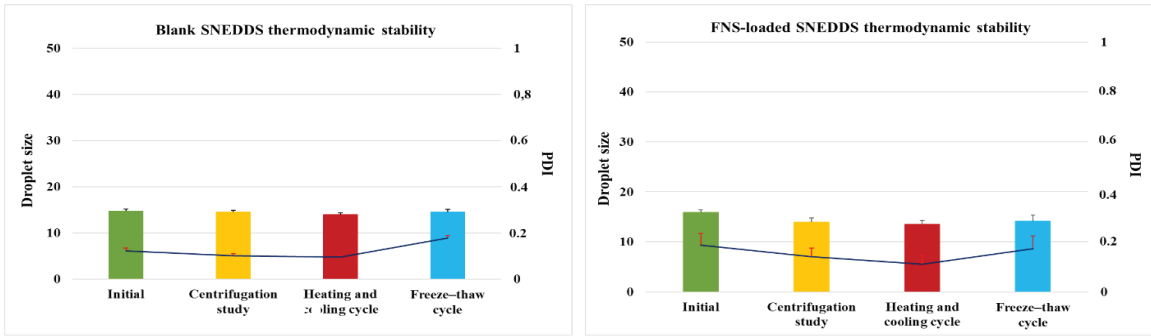


Figure 2. Thermodynamic stability results of blank and FNS-loaded SNEDDS (n=3, mean ± SD)

TEM examined structural and morphological characteristics of both blank and FNS-loaded SNEDDS. The images confirmed the formation of spherical nanoemulsion droplets with sizes ranging

from 10 to 100 nm, and drug loading did not compromise the structural integrity. Furthermore, the droplet size values obtained with the Malvern Zetasizer were consistent with TEM observations (Figure 3.).

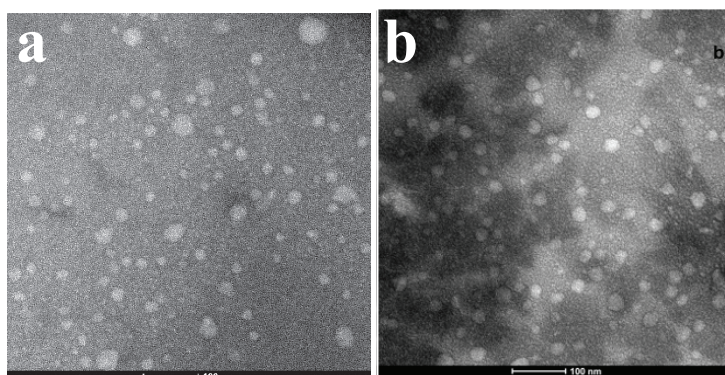


Figure 3. Morphology of a) blank and b) FNS-loaded SNEDDS

Stability studies of blank and FNS-loaded SNEDDS were performed over 6 months. Through long-term storage, the formulations remained physically stable, exhibiting no signs of turbidity or precipitation. Evaluations of 0, 1, 3, and 6 months under all storage conditions showed no statistically significant changes

in droplet size or PDI values ($p > 0.05$) (Figure 4.). Accordingly, both blank and FNS-loaded SNEDDS formulations were considered stable for at least 6 months under long-term ($25 \pm 2^\circ\text{C} / 60 \pm 5\% \text{ RH}$) and accelerated (4°C and $40 \pm 2^\circ\text{C} / 75 \pm 5\% \text{ RH}$) conditions.

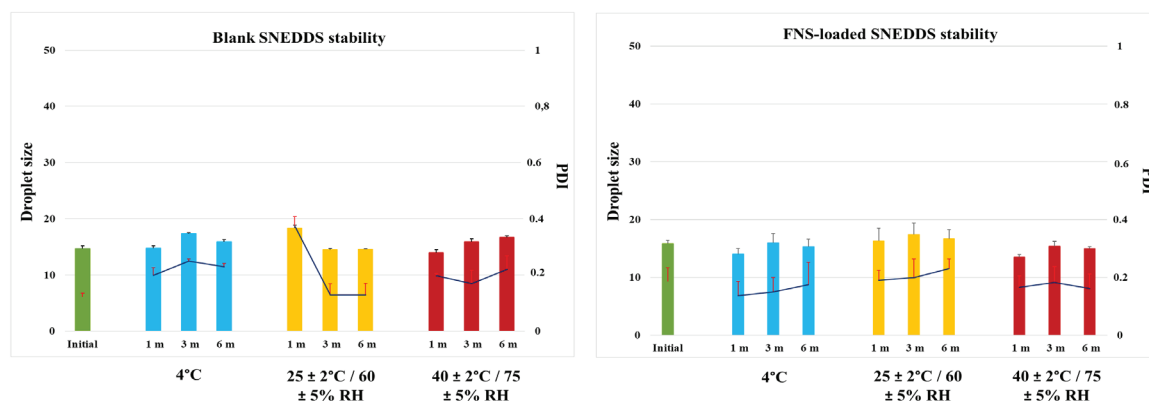


Figure 4. Stability results of blank and FNS-loaded SNEDDS formulations

Preparation and solid-state characterization of S-SNEDDS

Previous studies have reported the preparation of finasteride-loaded solid SNEDDS using spray-drying techniques (Fagir et al., 2015). Spray drying is an effective approach for converting liquid lipid-based systems into solid dosage forms; however, it generally requires specialized equipment and strict control of processing parameters. In the present study, an alternative solidification strategy based on adsorption onto a porous carrier was employed. The optimized FNS-load-

ed SNEDDS was converted into an S-SNEDDS by adsorption onto Neusilin® US2. Compared with spray drying, the adsorption technique represents a simpler and more cost-effective process that can generate free-flowing powders with high liquid-loading capacity through a straightforward mixing procedure (Beg et al., 2016). These characteristics make adsorption onto porous carriers an attractive approach for the development of solid SNEDDS formulations.

A major challenge in developing S-SNEDDS is achieving acceptable flow properties, which are critical

for process and dosage form uniformity. Since powder flowability is a complex characteristic influenced by multiple interrelated factors, it cannot be adequately described by a single parameter, and adequate powder flowability is a key requirement for the scale-up process of solid dosage forms, as it ensures uniform material feeding, consistent capsule filling, and minimal variability in dose content (Gamal et al., 2017).

Therefore, bulk and tapped density, angle of repose, and Hausner ratio were evaluated to characterize the solid-state properties of the FNS-loaded S-SNEDDS. To optimize the solidification process, three different SNEDDS-to-Neusilin® US2 ratios (1:1, 1.5:1, and 2:1) were investigated. Powder characterization studies were conducted in accordance with EP 11.0 (Sections 2.9.34 and 2.9.36). The results are given in Table 4.

Table 4. Micromeritic results of FNS-loaded SNEDDS: Neusilin® US2 powder

	1:1	1.5:1	2:1
Bulk density (g/mL)	0.26	0.33	0.41
Tapped density (g/mL)	0.38	0.46	0.55
Hausner's ratio	1.46	1.40	1.34
Angle of repose	32	36.9	38.3

Bulk and tapped density increased with increasing SNEDDS content. The 2:1 ratio exhibited the highest bulk density (0.41 g/mL) and tapped density (0.55 g/mL), indicating more efficient particle packing and reduced inter-particulate void spaces. This behavior is likely attributable to improved pore filling of the Neusilin® US2 structure at higher liquid loadings, resulting in denser, more coherent powder assemblies. In contrast, the 1:1 formulation showed the lowest density values, suggesting incomplete adsorption of the liquid SNEDDS and a more porous powder structure, which may negatively affect flow behavior and content uniformity during capsule filling. Angle of repose values ranged from 32° to 38.3°, corresponding to acceptable flow properties according to EP 11.0 criteria (25°– 40°). The 1:1 formulation exhibited the lowest angle of repose, suggesting relatively better flow behavior; however, this observation must be interpreted in conjunction with other flow indicators. The 2:1 formulation, despite a slightly higher angle of repose (38.3°), demonstrated faster flow time and remained within acceptable limits. A progressive decrease in the Hausner ratio was observed with increasing SNEDDS content, with values of 1.46, 1.40, and 1.34 for the 1:1, 1.5:1, and 2:1 ratios, respectively. According to the pharmacopoeia, Hausner ratio values between 1.26 and 1.34 indicate moderate flowability, whereas val-

ues above 1.35 indicate poor flowability. From this perspective, the 2:1 formulation exhibited the most favorable flow behavior among the tested ratios. Considering all solid-state characterization parameters, the FNS-loaded SNEDDS with an SNEDDS: Neusilin® US2 ratio of 2:1 was identified as the most suitable composition. This formulation provided an optimal balance among high liquid-loading capacity, acceptable powder flow properties, and suitability for capsule formulation. Nevertheless, to ensure a comprehensive evaluation of the influence of SNEDDS loading on solid-state characteristics and formulation performance, all three ratios were subjected to further solid-state characterization studies before final selection for capsule development. The solid-state properties of FNS, Neusilin® US2, blank S-SNEDDS (1:1, 1.5:1, and 2:1), and FNS-loaded S-SNEDDS (1:1, 1.5:1, and 2:1) formulations were also investigated using SEM, DSC, FTIR, and XRPD to elucidate the physical state of the drug and its interaction with the solid carrier.

SEM analysis revealed that pure FNS consisted of irregularly shaped crystalline particles with rough surface morphology, whereas Neusilin® US2 exhibited spherical particles with smooth surfaces (Figure 5.). Both blank and FNS-loaded S-SNEDDS formulations retained the characteristic spherical morpholo-

gy of Neusilin® US2, and no crystalline drug particles were observed on the surface of the adsorbent at any SNEDDS-to-carrier ratio. The absence of visible drug crystals indicates that FNS was fully solubilized in the

SNEDDS and successfully adsorbed onto the porous structure of Neusilin® US2, consistent with previously reported S-SNEDDS systems employing inorganic porous carriers (Kim et al., 2021).

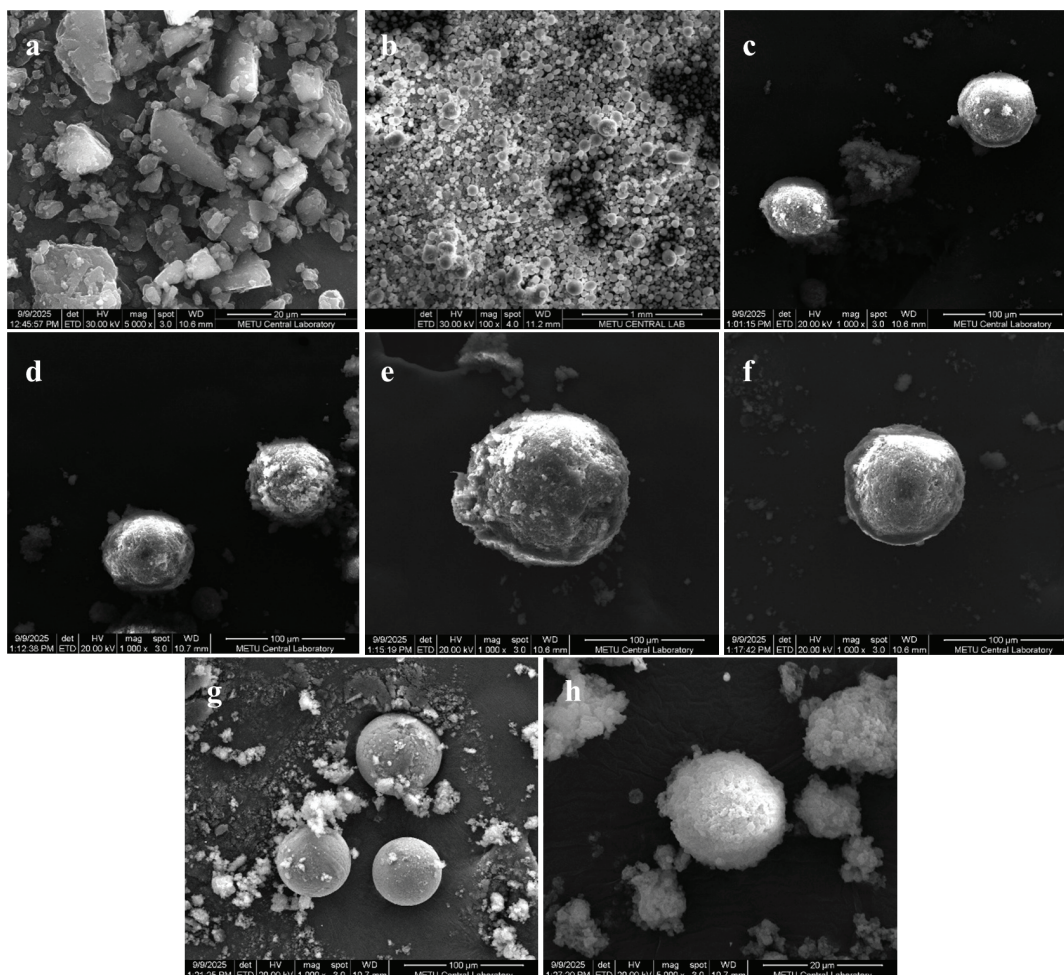


Figure 5. The morphology of a) FNS (5000x), b) Neusilin® US2 (100x), c) Blank S-SNEDDS 1:1 (1000x), d) Blank S-SNEDDS 1.5:1 (1000x), e) Blank S-SNEDDS 2:1 (1000x), f) FNS-loaded S-SNEDDS 1:1(1000x), g) FNS-loaded S-SNEDDS 1.5:1 (1000x), h) FNS-loaded S-SNEDDS 2:1 (5000x)

DSC thermogram of pure FNS showed a distinct endothermic melting peak (261 °C) *corresponding to its crystalline structure* (Figure 6.) (Wang et al., 2023). This characteristic thermal event was absent in all FNS-loaded S-SNEDDS formulations, while no additional endothermic or exothermic peaks were detected (Figure 6.). The disappearance of the FNS melting peak confirms the loss of crystallinity. It suggests that the drug was molecularly dispersed or present in an amorphous state with-

in the SNEDDS adsorbed onto Neusilin® US2. Similar DSC behavior has been reported for various S-SNEDDS formulations and is considered indicative of successful drug incorporation without surface precipitation (Abd-Elhakeem et al., 2019). Moreover, the absence of unexpected thermal transitions suggests that there are no physicochemical incompatibilities between FNS and the excipients, a prerequisite for the development of stable S-SNEDDS formulations (Bhagwat et al., 2021).

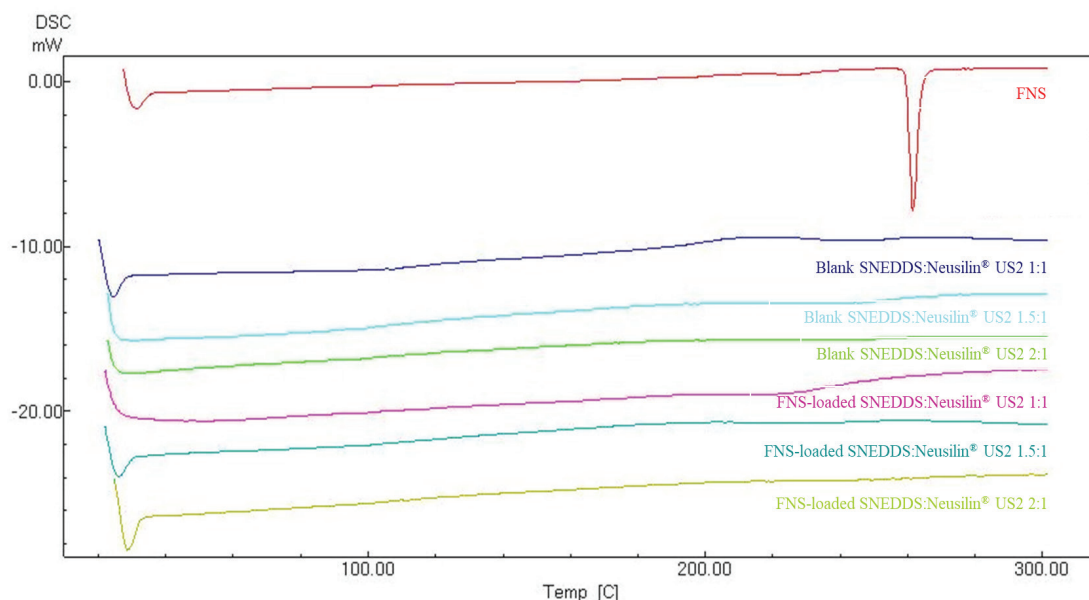


Figure 6. DSC thermograms of FNS, blank, and FNS-loaded S-SNEDDS (1:1, 1.5:1, 2:1)

Determining the specific peaks of the active substance using FTIR spectroscopy is important for interpreting structural changes that may occur during formulation studies. A carbonyl (C=O) peak at 1666 cm^{-1} , resulting from stretching vibrations corresponding to the two characteristic amide groups of FNS, and peaks corresponding to characteristic amide bands (N-H) at 3429 cm^{-1} and 1600 cm^{-1} , resulting from stretching and bending vibrations, were observed. The bands at 1364 and 1383 cm^{-1} belong to the tert-butyl group (Figure 7.). (Irfan et al., 2023; Li et al., 2024). The characteris-

tic absorption bands of FNS in the $3500\text{--}2500\text{ cm}^{-1}$ region were masked by the more intense bands originating from the SNEDDS components. No new peaks or significant shifts were observed in the spectra of FNS-loaded S-SNEDDS compared to those of the corresponding blank formulations. The similarity between the spectra of blank and drug-loaded systems indicates that FNS did not undergo chemical interaction with the excipients during solidification and was physically adsorbed onto the carrier matrix, in agreement with previously published findings (Wu et al., 2025).

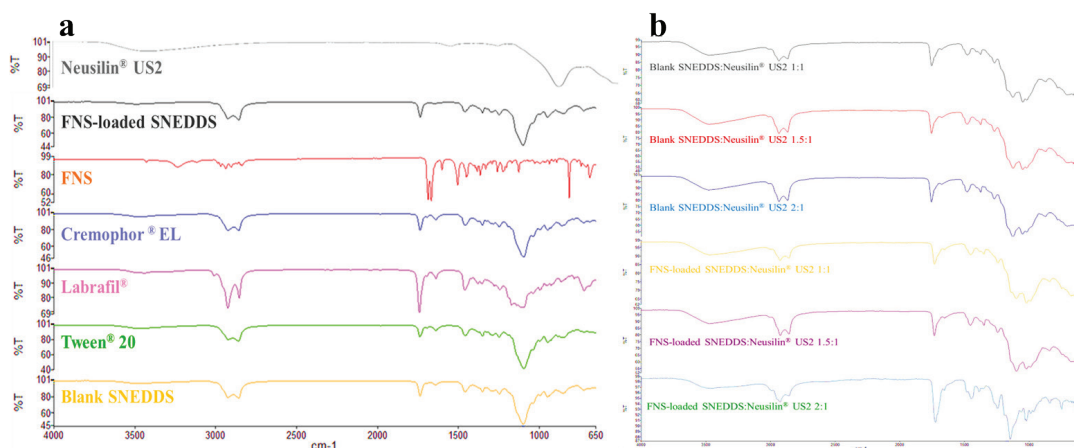


Figure 7. FTIR spectrum of a) FNS, Neusilin® US2, SNEDDS excipients, blank, and FNS-loaded SNEDDS, b) blank and FNS-loaded S-SNEDDS (1:1, 1.5:1, 2:1)

XRPD analysis also supported the solid-state transformation of FNS. XRPD analysis performed on FNS confirmed the crystal structure with distinct and strong diffraction peaks at major angles of 13.8°, 14.2°, 15.4°, 15.7°, 16.7°, 19.6°, 19.8°, and 20.6° at 2 θ (Figure 8.) (Wang et al., 2023). In contrast, Neusilin® US2 did not show a distinct diffraction peak, confirming its amorphous structure (Figure 8.) (Dangre et al.,

2021). The absence of characteristic FNS diffraction peaks in all FNS-loaded S-SNEDDS formulations demonstrates the conversion of FNS from a crystalline to an amorphous or molecularly dispersed state within the SNEDDS matrix. This loss of crystallinity upon solidification of SNEDDS has been widely reported and is associated with improved dissolution and bioavailability performance (Usta et al., 2023).

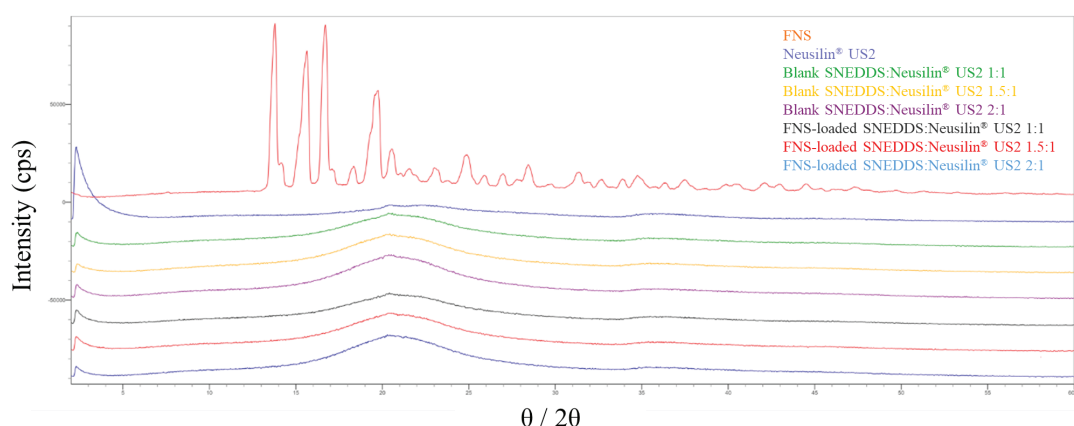


Figure 8. XRPD patterns of FNS, Neusilin® US2, blank and FNS-loaded S-SNEDDS (1:1, 1.5:1, 2:1)

Preparation and characterization of FNS-loaded S-SNEDDS capsules

Based on micromeritic evaluations and solid-state characterization, the formulation consisting of FNS-loaded SNEDDS adsorbed onto Neusilin® US2 at a 2:1 ratio was selected as the optimal system. The resulting free-flowing powder was filled into size 00el hard gelatin capsules (Capsugel®, Belgium). Each capsule was formulated to be equivalent to the reference product Propecia® 1 mg film-coated tablet and contained 1 mg of FNS incorporated into 0.4 g of SNEDDS and adsorbed onto 0.2 g of Neusilin® US2.

Quality control tests conducted on the prepared capsules demonstrated compliance with the EP 11.0 specifications. Drug content analysis showed an average FNS content of 1.03 mg per capsule, corresponding to 103% of the labeled amount. Weight variation testing confirmed that all capsules fell within 90–110% of the mean capsule weight. Disintegration testing revealed complete disintegration within 3.6 ± 0.05 min-

utes. All evaluated parameters were within EP 11.0 acceptance limits (2.9.1, 2.9.5, and 2.9.6).

The reconstitution performance of the S-SNEDDS capsules was evaluated by dispersing the capsule contents in aqueous media. The resulting nanoemulsions exhibited a mean droplet size of 17.5 ± 1.08 nm with a PDI of 0.226 ± 0.040 . These values were not statistically different from those of the corresponding FNS-loaded SNEDDS (15.9 ± 0.55 nm; PDI: 0.194 ± 0.041 ; $p > 0.05$), indicating that the solidification and encapsulation processes did not adversely affect the self-nanoemulsifying properties of the formulation. Similar findings have been reported for solidified SNEDDS systems prepared using porous adsorbents (Kim et al., 2021).

Stability studies were performed under different storage conditions, including 4 °C / 25 ± 2 °C / 60 ± 5 % RH, and 40 ± 2 °C / 75 ± 5 % RH, for up to 6 months. The FNS-loaded S-SNEDDS capsules remained physically and chemically stable at 4 °C and 25 ± 2 °C / 60

$\pm 5\%$ RH, with drug content values remaining within the acceptable range of 85–115% (Table 5.). Under accelerated conditions ($40 \pm 2^\circ\text{C}$ / $75 \pm 5\%$ RH), a statistically significant decrease in drug content was observed at 6 months, exceeding pharmacopeial limits. These results indicate that the developed formula-

tion demonstrates adequate stability under long-term and intermediate storage conditions but is sensitive to high temperature and humidity, which is consistent with previously reported lipid-based solid dosage forms.

Table 5. Stability of S-SNEDDS capsules

	4 °C	25 ± 2 °C / %60 ± 5 RH	40 ± 2 °C / %75 ± 5 RH
Initial*	%103 ± 1.09		
3 m*	%103 ± 3.31	%101 ± 1.09	%90.2 ± 16.4
6 m*	%96.0 ± 0.93	%95.2 ± 10.5	%36.9 ± 8.0

***In vitro* dissolution studies**

In vitro dissolution studies demonstrated that no statistically significant difference was observed among FNS powder, FNS-loaded SNEDDS, S-SNEDDS capsules, and the reference Propecia® tablet in pH 7.4 PBS containing 0.5% SLS, where more than 80% of the drug was released within 30 min, and comparable cumulative dissolution profiles were obtained at 120 min (Figure 9.). This behavior can be attributed to the presence of SLS in the dissolution medium, which enhances the apparent solubility of poorly water-soluble drugs through improved wettability and micellar solubilization (Incecayir et al., 2021; Ng et al., 2016). Consequently, the discriminatory power of this medium was limited, and all formulations exhibited rapid and extensive drug release. To better predict *in vivo* performance, dissolution studies were additionally conducted in FaSSIF-V2. Although FNS is known to exhibit minimal food-dependent absorption, the fasted-state medium was deliberately selected because it represents a more standardized and physiologically reproducible intestinal environment with lower bile salt and lipid content. Under such conditions, formulation-related differences in drug release are more sensitively detected. In contrast, the confounding vari-

ability associated with fed-state conditions-such as increased bile secretion, delayed gastric emptying, and fluctuating intestinal fluid composition-is minimized. Therefore, FaSSIF-V2 provides a conservative, biorelevant platform for evaluating lipid-based delivery systems and establishing *in vitro-in vivo* relevance. In FaSSIF-V2, FNS-loaded S-SNEDDS capsules exhibited slower initial dissolution than the reference Propecia® tablet, which showed rapid early release (>90% within 15-20 min). Nevertheless, drug release from the S-SNEDDS capsules increased progressively and reached nearly complete dissolution within 90 min, resulting in comparable dissolution extents for both formulations at later time points. The initially slower release from S-SNEDDS was attributed to the desorption-controlled release of SNEDDS from the porous Neusilin® US2 matrix and the comparable size of the formed nanoemulsion droplets to the pore diameter of the adsorbent, which may transiently delay emulsification (Usta et al., 2023). Overall, these findings indicate that while S-SNEDDS modulates the early release phase, it ultimately completes drug release under biorelevant fasted-state conditions, supporting its suitability for the oral delivery of an FNS-loaded S-SNEDDS capsule.

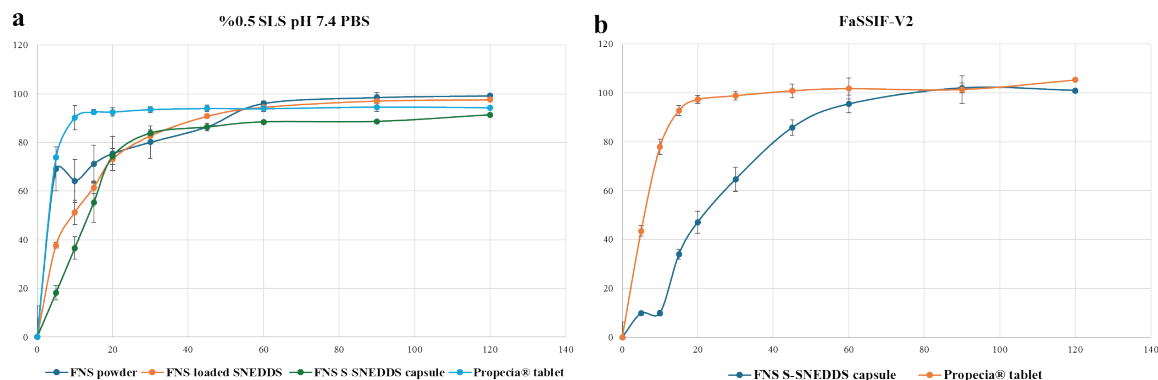


Figure 9. *In vitro* dissolution profiles of a) FNS powder, Propecia® tablets, FNS-loaded SNEDDS, and S-SNEDDS capsules in a pH 7.4 PBS medium containing 0.5% SLS, b) Propecia® tablets and FNS-loaded S-SNEDDS capsules in FaSSIF-V2 (n=3, mean±SD)

CONCLUSION

In this study, a Neusilin® US2-based S-SNEDDS was successfully developed for the oral delivery of FNS, a poorly water-soluble BCS Class II drug. The optimized SNEDDS formulation composed of Labrafil®, Cremophor® EL, and Tween® 20 exhibited rapid self-nanoemulsification, small droplet size, low polydispersity index, and high thermodynamic stability. Drug loading did not significantly alter the physicochemical properties of the system. Solidification via adsorption onto Neusilin® US2 produced free-flowing powders with acceptable micromeritic properties, with the 2:1 SNEDDS-to-carrier ratio identified as optimal. Solid-state analyses (DSC, XRPD, FTIR, and SEM) confirmed that FNS was present in an amorphous or molecularly dispersed state within the porous carrier matrix, indicating effective drug stabilization without evidence of recrystallization or chemical interaction. The optimized S-SNEDDS capsules met EP 11.0 quality requirements and preserved the self-nanoemulsifying performance upon reconstitution. *In vitro* dissolution studies showed that drug release is relative to the reference product. The developed Neusilin® US2-based S-SNEDDS represents a promising solid oral delivery platform for FNS, with improved formulation stabil-

ity, better handling characteristics, and the potential for dose reduction. This approach may help minimize systemic adverse effects and improve long-term patient adherence in the management of androgenetic alopecia.

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AUTHOR CONTRIBUTION STATEMENT

Concept: D.Y.U., F.N.Ö.; Design: D.Y.U.; Control: D.Y.U., F.N.Ö., G.B., S.İ.T.; Sources: D.Y.U., F.N.Ö., S.İ.T.; Materials: D.Y.U., F.N.Ö., S.İ.T.; Data Collection and/or Processing: D.Y.U., F.N.Ö., G.B., S.İ.T.; Analysis and/or Interpretation: D.Y.U., F.N.Ö., G.B.; Literature Review: D.Y.U., G.B.; Manuscript Writing: D.Y.U., G.B., S.İ.T.; Critical Review: D.Y.U., S.İ.T.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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