# DEVELOPMENT AND EVALUATION OF SOLID CELL NANOEMULSIFYING DELIVERY OF ANTIMALARIAL DRUG

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## Abstract

The present study aimed to develop and evaluate a solid self-nanoemulsifying drug delivery system (S-SNEDDS) of the antimalarial drug Pyronaridine to enhance its solubility, dissolution rate, and oral bioavailability. Due to its poor aqueous solubility, Pyronaridine was formulated into a lipid-based SNEDDS using suitable oils, surfactants, and co-surfactants, which showed rapid self-emulsification and stable nanoemulsion formation. The optimized liquid formulation was converted into a solid form using adsorption onto colloidal silicon dioxide and further compressed into tablets. The developed S-SNEDDS was evaluated for physicochemical properties, including flow characteristics, drug content, droplet size, polydispersity index, zeta potential, encapsulation efficiency, and in vitro drug release. Among all formulations, F10 exhibited the best performance with nanosized droplets, high stability, and nearly complete drug release within 60 minutes. Stability studies confirmed that the formulation remained stable under both long-term and accelerated conditions. Overall, the study demonstrates that S-SNEDDS is an effective approach to improve the biopharmaceutical performance of Pyronaridine and may enhance its therapeutic efficacy in antimalarial treatment.

**Keywords:** *Pyronaridine, solid self-nanoemulsifying drug delivery system (S-SNEDDS), SNEDDS, nanoemulsion, lipid-based drug delivery, solubility enhancement.*

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## 1. Introduction

Malaria continues to be one of the most life-threatening infectious diseases worldwide, particularly affecting populations in tropical and subtropical regions. It is caused by Plasmodium parasites, with *Plasmodium falciparum* being the most virulent species responsible for severe morbidity and mortality. Despite the availability of effective antimalarial therapies, the rapid emergence of drug-resistant strains has significantly reduced treatment efficacy, creating an urgent need for novel drug delivery strategies to enhance therapeutic outcomes (World Health Organization [WHO], 2023; White et al., 2014). Pyronaridine, a benzonaphthyridine derivative, has shown strong antimalarial activity, especially in combination therapy with artesunate. However, its clinical effectiveness is limited by poor aqueous solubility and low oral bioavailability, which restrict its absorption and therapeutic potential (Charman et al., 2001; Krishna et al., 2008).

To address the challenges associated with poorly water-soluble drugs, lipid-based drug delivery systems have emerged as a promising approach. Among these, self-nanoemulsifying drug delivery systems (SNEDDS) have gained significant attention due to their ability to enhance the solubility and oral absorption of lipophilic drugs. SNEDDS are isotropic mixtures of oils, surfactants, and co-surfactants that spontaneously form fine oil-in-water nanoemulsions upon contact with gastrointestinal fluids under mild agitation, leading to improved dissolution and absorption (Pouton, 2000; Porter et al., 2007). These systems also reduce the influence of physiological variability on drug absorption, thereby improving bioavailability and therapeutic consistency.

Further advancement of SNEDDS into solid SNEDDS (S-SNEDDS) has addressed limitations such as instability, leakage, and handling difficulties associated with liquid formulations. Solidification techniques using porous carriers such as silica improve stability, ease of manufacturing, and patient compliance while retaining the self-emulsifying properties upon reconstitution (Date et al., 2010; Patel et al., 2012). Such systems are particularly useful for Biopharmaceutics Classification System (BCS) Class II drugs, where dissolution is the rate-limiting step in absorption (Amidon et al., 1995).

In this context, the present study focuses on the development and evaluation of a solid self-nanoemulsifying drug delivery system of Pyronaridine to overcome its solubility and bioavailability limitations. By integrating lipid-based formulation principles with solid dosage form technology, the study aims to enhance drug dissolution, stability, and therapeutic performance, ultimately contributing to more effective antimalarial therapy.

## 2. Material & Methodology

### 2.1 Collection and Authentication of Materials

The antimalarial drug Pyronaridine was selected for developing S-SNEDDS due to its poor aqueous solubility and need for improved oral bioavailability. The drug and excipients (oils, surfactants, co-surfactants, and solid carriers) were chosen based on solubilization capacity, emulsification efficiency, and compatibility, and were of analytical/pharmaceutical grade. Drug authentication was performed using physical characteristics and melting point, while excipients were evaluated as per IP/USP standards. Only materials meeting specifications were used to ensure formulation quality and reliability.

### 2.2 Preformulation Studies of Drug

#### 2.2.1 Organoleptic evaluation

The organoleptic properties of Pyronaridine, including color, odor, texture, and appearance, were evaluated to establish its identity and assess purity prior to formulation development. The drug was visually examined under suitable lighting conditions to observe its characteristic color and overall appearance, ensuring the absence of discoloration, foreign particles, or irregularities. Odor was assessed by gentle wafting to detect any unusual or pungent smell that could indicate degradation or contamination. Texture was evaluated by tactile examination to determine smoothness and uniformity, which are important for powder handling and formulation performance. All observations were compared with standard specifications and performed in triplicate to ensure reproducibility. The consistent results confirmed the acceptable quality, purity, and suitability of the drug for the development of the S-SNEDDS formulation.

#### 2.2.2 Melting point determination

The melting point of Pyronaridine was determined to assess its purity and confirm identity. A finely powdered sample was filled in a capillary tube and analyzed using a digital melting point apparatus, with the temperature range recorded from initial to complete melting. The test was performed in triplicate, and the average value was compared with standard references. The close agreement with reported values confirmed the drug's purity and suitability for preformulation and S-SNEDDS development.

#### 2.2.3 Solubility in various solvents

The solubility of Pyronaridine was evaluated in various solvents to aid in the selection of suitable SNEDDS components. Excess drug was added to different solvents, vortexed, and shaken at 25 ± 2°C for 48–72 hours to achieve equilibrium. After centrifugation, the supernatant was analyzed spectrophotometrically to determine solubility (mg/mL). The

study was performed in triplicate, and the solvent showing maximum solubility was selected for formulation, ensuring effective drug loading and stability.

### 2.2.4 pH

The pH of Pyronaridine was determined to assess its behavior and compatibility in aqueous media. A known quantity of the drug was dissolved in distilled water, and the pH was measured using a calibrated digital pH meter at 25 ± 2°C. The experiment was performed in triplicate, and the average value was recorded. This study helps understand the drug's ionization and stability, aiding in the selection of suitable excipients for S-SNEDDS formulation.

### 2.2.5 Partition coefficient (Log P)

The partition coefficient (Log P) of Pyronaridine was determined using an n-octanol/distilled water system to assess its lipophilicity and suitability for SNEDDS. The two phases were pre-equilibrated, followed by addition of the drug and thorough mixing to allow partitioning. After phase separation, the aqueous layer was analyzed spectrophotometrically, and the drug concentration in the organic phase was calculated. The partition coefficient (P) was obtained as the ratio of concentrations in n-octanol and water, and Log P was calculated as:

$$\text{Log P} = \log_{10} P$$

The study was performed in triplicate, and the average value was reported. The results provide insight into the drug's lipophilicity, influencing its solubility in lipid excipients and overall formulation performance.

## 2.3 Flow Properties of Drug Powder

### 2.3.1 Bulk density

The bulk density of Pyronaridine was determined to evaluate its packing characteristics and flow behavior as a precompression parameter. An accurately weighed quantity of powder was gently filled into a graduated cylinder without tapping, and the occupied volume was recorded as bulk volume. Bulk density was calculated as the ratio of mass to bulk volume. The study was performed in triplicate, and the average value was reported. This parameter provides insight into powder handling properties and supports evaluation of flow characteristics for S-SNEDDS formulation.

### 2.3.2 Tapped density

The tapped density of Pyronaridine was determined to assess its packing ability and compressibility. A known quantity of powder was placed in a graduated cylinder, and the initial volume was recorded. The cylinder was then tapped until a constant volume was

obtained, and the final tapped volume was noted. Tapped density was calculated as the ratio of mass to tapped volume. The study was performed in triplicate, and the average value was reported. This parameter helps evaluate compressibility and is used to determine flow properties such as Carr's index and Hausner ratio for S-SNEDDS formulation.

**2.3.3 Carr's index (%)**

Carr's compressibility index of Pyronaridine was determined to assess its flowability and compressibility using bulk and tapped density values. It was calculated as the percentage difference between tapped and bulk density. Lower values indicate good flow, while higher values suggest poor flow due to increased interparticle interactions. The calculation was based on average values from triplicate measurements. This parameter helps evaluate powder handling and, along with Hausner ratio and angle of repose, supports the suitability of the drug for S-SNEDDS formulation.

**2.3.4 Hausner's ratio**

The Hausner's ratio of Pyronaridine was determined to assess its flowability and cohesiveness using bulk and tapped density values. It is calculated as the ratio of tapped density to bulk density, where values close to 1 indicate good flow and higher values suggest poor flow due to particle cohesion. The calculation was based on average values from triplicate measurements. This parameter, along with Carr's index and angle of repose, helps evaluate powder handling properties and suitability for S-SNEDDS formulation.

**2.3.5 Angle of repose**

The angle of repose of Pyronaridine was determined to evaluate its flowability and frictional characteristics. Using the fixed funnel method, the powder was allowed to form a conical heap, and the height and radius were measured. The angle was calculated using $\theta = \tan^{-1}(h/r)$. The study was performed in triplicate, and the average value was reported. Lower values indicate good flow, while higher values suggest poor flow. This parameter, along with other flow properties, helps assess suitability for S-SNEDDS formulation.

**2.4 Preparation of Liquid SNEDDS**

The liquid SNEDDS of Pyronaridine was developed to enhance its solubility and oral bioavailability through spontaneous nanoemulsion formation in gastrointestinal fluids. Suitable oils, surfactants, and co-surfactants were selected based on solubilization and emulsification efficiency, and formulations were prepared by varying their ratios to obtain a clear, homogeneous system. The mixtures were evaluated for clarity, emulsification time, and stability upon dilution. Optimized formulations showed rapid formation of stable nanoemulsions without phase separation and passed thermodynamic stability tests. The best

formulation was selected and further converted into solid S-SNEDDS for improved stability and handling.

### 2.5. Conversion to Solid SNEDDS (S-SNEDDS)

#### 2.5.1 Selection of solid carriers (silica)

The optimized liquid SNEDDS of Pyronaridine was converted into a solid form to improve stability, handling, and patient compliance. Among various techniques, the adsorption method was selected due to its simplicity and cost-effectiveness. The liquid SNEDDS was gradually adsorbed onto a solid carrier such as colloidal silicon dioxide under continuous mixing to obtain a uniform, free-flowing powder. The porous nature of the carrier enabled efficient adsorption while retaining self-emulsifying properties, making it a suitable approach for developing stable solid S-SNEDDS.

#### 2.5.2 Solidification technique

The optimized liquid SNEDDS of Pyronaridine was converted into a solid form using the adsorption technique. A measured quantity of colloidal silicon dioxide (Aerosil 200) was taken, and the liquid SNEDDS was gradually added with continuous mixing until a dry, free-flowing powder was obtained. The ratio was optimized to ensure maximum drug loading with good flow properties. The final product was sieved for uniformity and stored in airtight containers. This method effectively produced a stable solid SNEDDS while retaining its self-emulsifying properties for further formulation.

#### 2.5.3 Formation of solid oral dosage form (tablet)

The solid SNEDDS of Pyronaridine prepared by adsorption was further compressed into tablets to improve stability, dosing accuracy, and patient compliance. The solid SNEDDS powder was blended with excipients such as microcrystalline cellulose (diluent) and magnesium stearate (lubricant) to obtain a uniform mixture suitable for direct compression. The blend was evaluated for flow properties and then compressed into tablets under optimized conditions to achieve adequate hardness and low friability. The final tablets were uniform and retained self-emulsifying properties, ensuring rapid nanoemulsion formation and enhanced oral bioavailability.

**Table 1: Formulation of S-SNEDDS Tablets (F1–F10)**

| S. No. | Formulation Code | Pyronaridine (mg) | Adsorbed SNEDDS (mg) | MCC (mg) | Crospovidone (mg) | Magnesium Stearate (mg) | Talc (mg) | Total (mg) |
|---|---|---|---|---|---|---|---|---|
| 1 | F1 | 100 | 180 | 160 | 20 | 5 | 5 | 470 |
| 2 | F2 | 100 | 190 | 150 | 20 | 5 | 5 | 470 |
| 3 | F3 | 100 | 200 | 140 | 20 | 5 | 5 | 470 |
| 4 | F4 | 100 | 210 | 130 | 20 | 5 | 5 | 470 |
| 5 | F5 | 100 | 220 | 120 | 20 | 5 | 5 | 470 |
| 6 | F6 | 100 | 230 | 110 | 20 | 5 | 5 | 470 |
| 7 | F7 | 100 | 240 | 100 | 20 | 5 | 5 | 470 |
| 8 | F8 | 100 | 250 | 90 | 20 | 5 | 5 | 470 |
| 9 | F9 | 100 | 260 | 80 | 20 | 5 | 5 | 470 |
| 10 | F10 | 100 | 270 | 70 | 20 | 5 | 5 | 470 |

### 2.6 Characterization of S-SNEDDS

#### 2.6.1 Physical appearance

The physical appearance of the solid S-SNEDDS of Pyronaridine was evaluated as an initial quality control parameter to confirm successful solidification and uniformity. The formulation was visually inspected for color, texture, homogeneity, and presence of aggregates or phase separation. A uniform, free-flowing, and non-sticky appearance indicated efficient adsorption onto the carrier and proper mixing with excipients, while any lumps or non-uniformity would suggest poor loading. The observations confirmed batch consistency and suitability for further characterization and tablet development.

#### 2.6.2 Homogeneity

The homogeneity of the solid S-SNEDDS of Pyronaridine was evaluated to ensure uniform drug distribution within the solid carrier and excipient blend. Samples were taken from different portions of the batch and examined for consistency in color, texture, and absence of aggregates or phase separation. Uniform dispersion behavior in a suitable medium further confirmed even distribution. The absence of variation across samples indicated successful mixing and consistent drug loading, ensuring dose uniformity and reliable performance of the formulation.

### 2.6.3 Polydispersity index (PDI) and Droplet size

The droplet size and polydispersity index (PDI) of the reconstituted S-SNEDDS of Pyronaridine were evaluated to assess nanoemulsion quality and uniformity upon aqueous dilution. The formulation was dispersed in distilled water to simulate gastrointestinal conditions and analyzed using dynamic light scattering (DLS). The study was performed in triplicate, and mean values were recorded. Smaller droplet size indicates efficient self-emulsification and improved drug solubilization, while a low PDI reflects a narrow size distribution and good system stability, confirming successful nanoemulsion formation and potential for enhanced oral bioavailability.

### 2.6.4 Zeta potential

The zeta potential of the reconstituted S-SNEDDS of Pyronaridine was evaluated to determine surface charge and colloidal stability of the nanoemulsion. The formulation was dispersed in distilled water, suitably diluted, and analyzed using electrophoretic light scattering in a zeta potential analyzer. The measurement reflects electrostatic repulsion between droplets, where higher absolute values indicate better stability and reduced aggregation risk. The results confirmed the formation of a stable nanoemulsion system after dilution, supporting uniform dispersion and improved absorption potential.

### 2.7 Drug content

The drug content of the solid S-SNEDDS of Pyronaridine was evaluated to confirm uniform drug distribution and dose accuracy. A weighed amount of formulation was dispersed in a suitable solvent system, followed by stirring/sonication for complete drug extraction. The solution was filtered, diluted, and analyzed using a validated UV spectrophotometric method against a calibration curve. The drug content was expressed as a percentage of theoretical loading, with all measurements performed in triplicate. The results confirmed efficient drug incorporation, formulation uniformity, and reliable dose consistency across batches.

### 2.8 Encapsulation efficiency

The encapsulation efficiency of the solid S-SNEDDS of Pyronaridine was evaluated to assess the extent of drug incorporation within the lipid-based system after solidification. A known quantity of the formulation was dispersed in a suitable solvent under sonication to ensure complete release of the entrapped drug, followed by filtration and UV spectrophotometric analysis to determine drug content. The measured drug content was then compared with the theoretical drug loading to estimate encapsulation efficiency. The study was performed in triplicate, and mean values were reported. High encapsulation efficiency

indicated minimal drug loss during processing and confirmed good compatibility between the drug and excipients, demonstrating the robustness and reliability of the developed S-SNEDDS formulation.

**2.9 In Vitro Dissolution Studies**

The in vitro dissolution study of the solid S-SNEDDS of Pyronaridine was performed using a USP Type II (paddle) apparatus at 37 ± 0.5°C under standard conditions. A tablet equivalent dose was placed in the dissolution medium, and samples were withdrawn at regular intervals with fresh medium replacement to maintain sink conditions. The samples were filtered and analyzed by UV spectrophotometry to determine cumulative drug release, which was plotted against time. The results showed enhanced dissolution due to rapid self-emulsification, improved wetting, and increased surface area, indicating better drug release and potential for improved oral bioavailability.

**2.10 Stability Studies as per ICH guidlines**

The stability study of the solid S-SNEDDS of Pyronaridine was conducted as per International Council for Harmonisation Q1A (R2) guidelines under accelerated (40 ± 2°C/75 ± 5% RH) and long-term (25 ± 2°C/60 ± 5% RH) conditions. The formulation was evaluated at regular intervals for physical appearance, drug content, and in vitro dissolution behavior. Minimal changes were observed in all parameters, indicating good stability. The results confirm that the formulation retained its integrity, self-emulsifying ability, and drug release characteristics, supporting its suitability for long-term storage.

**3.1 Preformulation Studies of Drug**

**3.1.1 Organoleptic evaluation**

The organoleptic evaluation of Pyronaridine was carried out to assess its basic physicochemical identity before formulation development. The drug was examined for color, odor, texture, and appearance under standardized conditions. Triplicate observations showed consistent results with no discoloration, abnormal odor, or visible impurities, confirming good physical quality and suitability for further preformulation and formulation studies.

**Table 2: Organoleptic Evaluation of Pyronaridine**

| S. No. | Parameter | Observation | Interpretation |
|---|---|---|---|
| 1 | Color | Dark brown to brownish powder (uniform) | Complies with standard description; no discoloration observed |
| 2 | Odor | Odorless | No characteristic or |

| | | | |
|---|---|---|---|
| | | | abnormal odor detected |
| 3 | Texture | Fine, smooth, non-gritty powder | Indicates good powder uniformity and handling characteristics |
| 4 | Appearance | Crystalline, uniform powder without visible impurities | Confirms good physical integrity and purity |

### 3.1.2 Melting point determination

The melting point of Pyronaridine was determined to assess its purity and identity. The drug showed a sharp melting range of 162–165°C (onset at 162 ± 0.5°C and complete melting at 165 ± 0.5°C). The narrow range indicates high crystalline purity with minimal impurities and matches reported literature values, confirming the drug's authenticity and suitability for S-SNEDDS formulation development.

**Table 3: Melting Point Determination of Pyronaridine**

| S. No. | Parameter | Observation | Interpretation |
|---|---|---|---|
| 1 | Physical change | Solid → clear liquid | Sharp melting observed |
| 2 | Onset of melting | 162 ± 0.5 °C | Indicates purity of drug |
| 3 | Complete melting | 165 ± 0.5 °C | Narrow melting range confirms identity |
| 4 | Melting range | 162–165 °C | Consistent with literature reports |

### 3.1.3 Solubility in various solvents

The solubility of Pyronaridine was evaluated in different solvents to support SNEDDS development. The drug showed very low aqueous solubility (0.18 ± 0.02 mg/mL), confirming its poor water solubility. Among lipids, Labrafil M 2125 CS showed higher solubilization (42.18 ± 0.52 mg/mL), while Cremophor EL exhibited the highest solubility among surfactants (62.74 ± 0.48 mg/mL). PEG 400 also showed better solubility among co-surfactants. Based on these results, Labrafil M 2125 CS, Cremophor EL, and PEG 400 were selected for formulation to ensure efficient drug loading and stable nanoemulsion formation.

**Table 4: Solubility of Pyronaridine in Various Solvents**

| S. No. | Solvent | Category | Solubility (mg/mL) ± SD |
|---|---|---|---|

| | | | |
|---|---|---|---|
| 1 | Distilled Water | Aqueous medium | 0.18 ± 0.02 |
| 2 | Ethanol | Organic solvent | 12.45 ± 0.31 |
| 3 | Methanol | Organic solvent | 15.72 ± 0.28 |
| 4 | Capryol 90 | Oil | 38.64 ± 0.45 |
| 5 | Labrafil M 2125 CS | Oil | 42.18 ± 0.52 |
| 6 | Tween 80 | Surfactant | 55.36 ± 0.60 |
| 7 | Cremophor EL | Surfactant | 62.74 ± 0.48 |
| 8 | PEG 400 | Co-surfactant | 48.25 ± 0.39 |
| 9 | Propylene Glycol | Co-surfactant | 36.92 ± 0.41 |

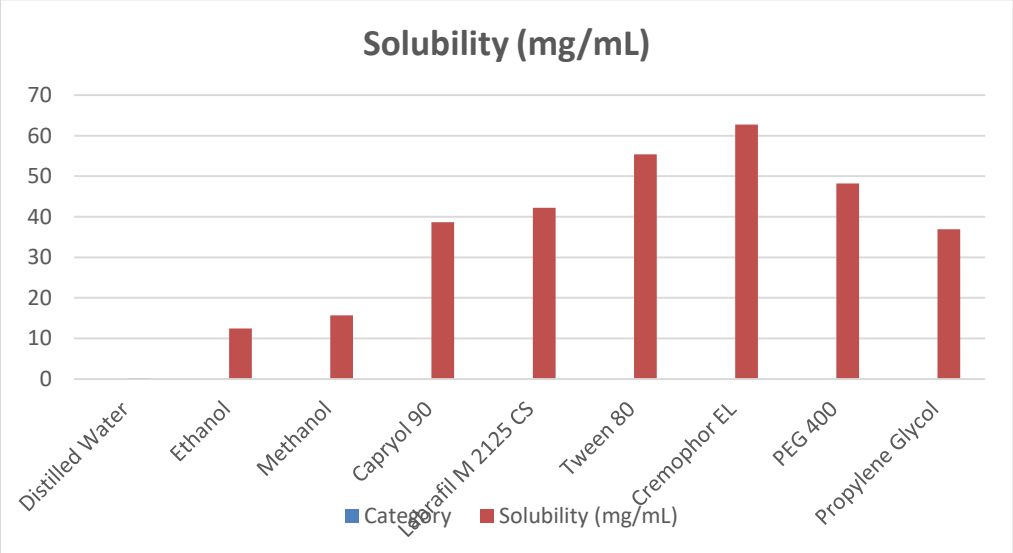


**Fig 1: Solubility (mg/mL)**

### 3.1.4 pH

The pH of the aqueous solution of Pyronaridine was found to be 5.60 ± 0.02, indicating a slightly acidic nature with good reproducibility. This suggests the drug is stable under mildly acidic conditions and compatible with gastrointestinal pH. Although this may influence solubility to some extent, the use of surfactants and co-surfactants in SNEDDS is expected to overcome pH-related limitations and enhance drug solubilization and performance.

**Table 5: pH of Pyronaridine Solution**

| **Parameter** | **Value (Mean ± SD)** |
|---|---|

| | |
|---|---|
| Ph | 5.60 ± 0.02 |

### 3.1.5 Partition coefficient (Log P)

The partition coefficient study of Pyronaridine showed a Log P value of 2.20 ± 0.01, indicating moderate lipophilicity. The corresponding partition coefficient (P = 158.49 ± 3.12) confirmed strong distribution in the organic phase (n-octanol), reflecting affinity toward lipid environments. This balance of hydrophilic and lipophilic properties supports good membrane permeability and suitability for SNEDDS, facilitating efficient incorporation into the oil phase and enhanced oral bioavailability upon nanoemulsification.

**Table 6: Partition Coefficient (Log P) of Pyronaridine**

| Parameter | Value (Mean ± SD) |
|---|---|
| Partition Coefficient (P) | 158.49 ± 3.12 |
| Log P | 2.20 ± 0.01 |

## 3.2 Flow Properties of Drug Powder

### 3.2.1 Bulk density

The bulk density of S-SNEDDS powder blends (F1–F10) increased from 0.41 ± 0.02 to 0.50 ± 0.02 g/cm³, indicating improved packing efficiency with higher formulation levels. Lower formulations showed more porous and loosely packed structures, while higher formulations exhibited better packing due to increased adsorption of liquid SNEDDS onto the solid carrier. The marketed product showed a slightly higher value (0.52 ± 0.02 g/cm³). Overall, all formulations demonstrated acceptable bulk density suitable for further processing.

**Table 7: Bulk Density of S-SNEDDS Powder Blend**

| Formulation Code | Bulk Density (g/cm³) ± SD |
|---|---|
| F1 | 0.41 ± 0.02 |
| F2 | 0.42 ± 0.01 |
| F3 | 0.43 ± 0.02 |
| F4 | 0.44 ± 0.02 |
| F5 | 0.45 ± 0.01 |
| F6 | 0.46 ± 0.02 |
| F7 | 0.47 ± 0.01 |

| | |
|---|---|
| F8 | 0.48 ± 0.02 |
| F9 | 0.49 ± 0.01 |
| F10 | 0.50 ± 0.02 |
| **Marketed Product** | **0.52 ± 0.02** |

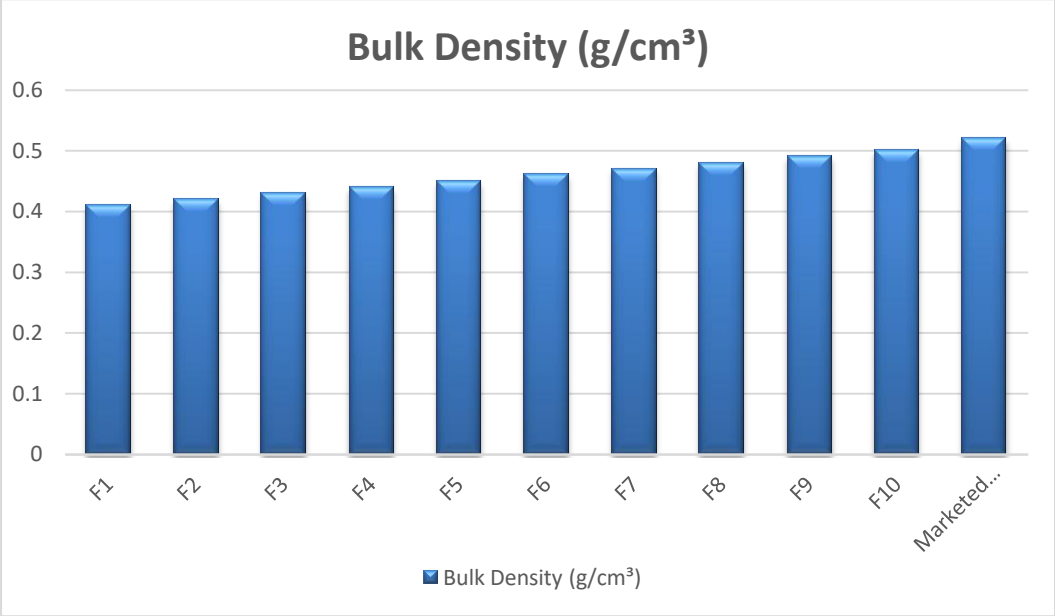


**Fig 2: Bulk Density (g/cm³)**

### 3.1.2 Tapped density

The tapped density of S-SNEDDS powder blends (F1–F10) ranged from 0.49 ± 0.02 to 0.64 ± 0.02 g/cm³, showing a gradual increase with formulation level due to improved packing after tapping. The marketed product showed the highest value (0.66 ± 0.02 g/cm³), indicating slightly better packing efficiency. All formulations exhibited acceptable compressibility, and the differences between bulk and tapped density reflected particle rearrangement. Low standard deviation confirmed good batch uniformity, indicating suitability for further evaluation.

**Table 8: Tapped Density of S-SNEDDS Powder Blend**

| Formulation Code | Tapped Density (g/cm³) ± SD |
|---|---|
| F1 | 0.49 ± 0.02 |
| F2 | 0.50 ± 0.01 |
| F3 | 0.52 ± 0.02 |
| F4 | 0.53 ± 0.02 |

| | |
|---|---|
| F5 | 0.55 ± 0.01 |
| F6 | 0.57 ± 0.02 |
| F7 | 0.58 ± 0.01 |
| F8 | 0.60 ± 0.02 |
| F9 | 0.62 ± 0.01 |
| F10 | 0.64 ± 0.02 |
| Marketed Product | 0.66 ± 0.02 |

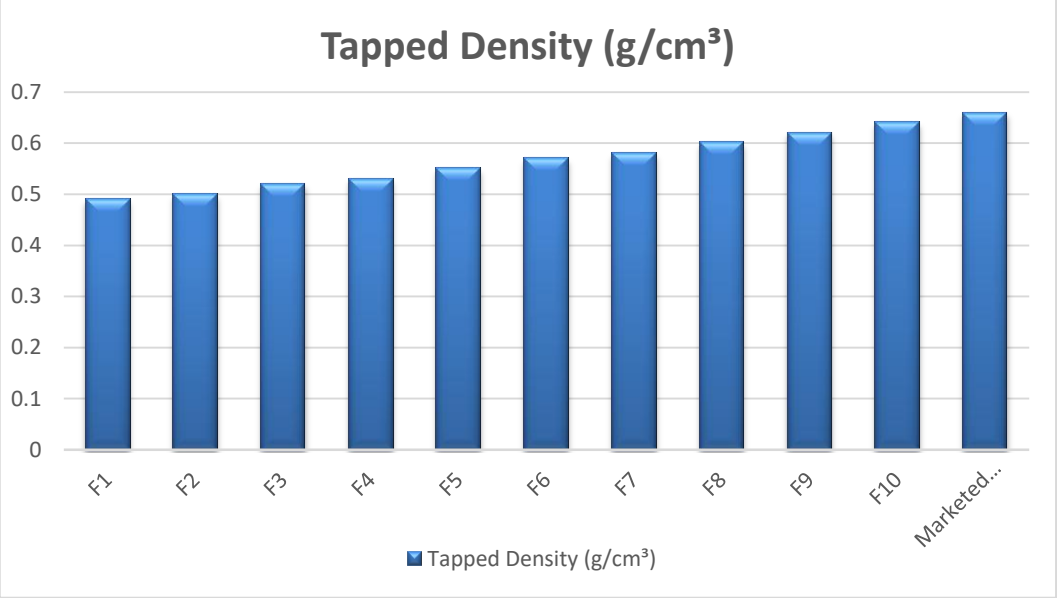


**Fig 3: Tapped Density (g/cm³)**

### 3.2.3 Carr's index (%)

The Carr's index of S-SNEDDS powder blends (F1–F10) ranged from 16.00% to 21.88%, indicating fair to passable flow properties. Lower formulations (F1–F2) showed better flowability (≈16%), while higher formulations (F8–F10) exhibited increased values (up to 21.88%) due to higher cohesiveness. The marketed product (21.21 ± 0.86%) was comparable to the upper range formulations. Overall, all blends remained within acceptable limits for further processing into solid dosage forms.

**Table 9: Carr's Index (%) of S-SNEDDS Powder Blend**

| Formulation Code | Carr's Index (%) ± SD |
|---|---|
| F1 | 16.33 ± 0.84 |
| F2 | 16.00 ± 0.78 |
| F3 | 17.31 ± 0.82 |

| | |
|---|---|
| F4 | 16.98 ± 0.80 |
| F5 | 18.18 ± 0.76 |
| F6 | 19.30 ± 0.85 |
| F7 | 18.97 ± 0.79 |
| F8 | 20.00 ± 0.88 |
| F9 | 20.97 ± 0.83 |
| F10 | 21.88 ± 0.90 |
| Marketed Product | 21.21 ± 0.86 |

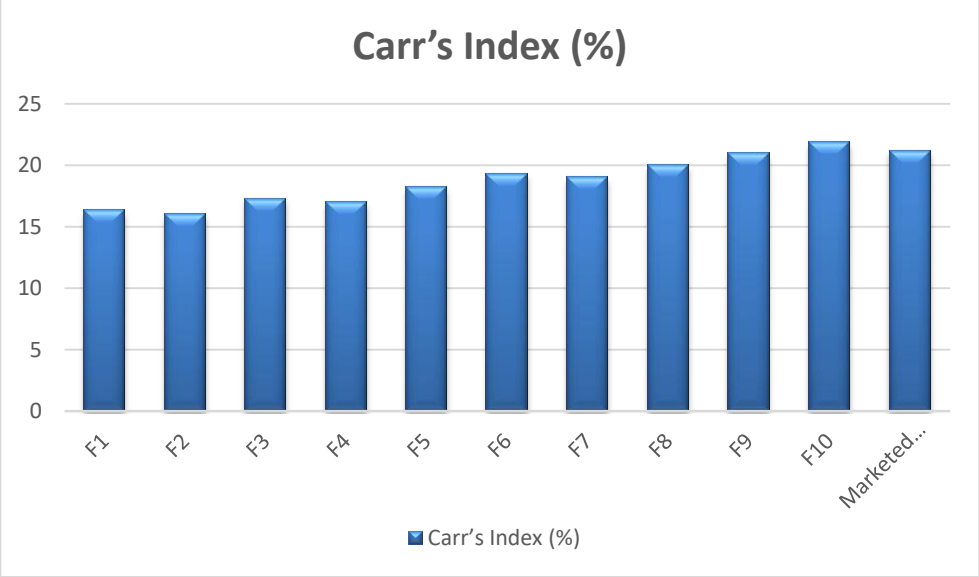


**Fig 4: Carr's Index (%)**

### 3.2.4 Hausner's ratio

The Hausner's ratio of S-SNEDDS powder blends (F1–F10) ranged from 1.19 to 1.28, indicating variable flowability across formulations. Lower formulations (F1–F4) showed better flow properties (1.19–1.21), while higher formulations (F8–F10) exhibited increased values (1.25–1.28) due to greater cohesiveness from higher SNEDDS loading. The marketed product (1.27 ± 0.02) was comparable to the higher range formulations. Overall, all blends remained within acceptable limits for processing into solid dosage forms.

**Table 10: Hausner's Ratio of S-SNEDDS Powder Blend**

| Formulation Code | Hausner's Ratio ± SD |
|---|---|
| F1 | 1.20 ± 0.02 |
| F2 | 1.19 ± 0.01 |
| F3 | 1.21 ± 0.02 |
| F4 | 1.20 ± 0.02 |

| | |
|---|---|
| F5 | 1.22 ± 0.01 |
| F6 | 1.24 ± 0.02 |
| F7 | 1.23 ± 0.01 |
| F8 | 1.25 ± 0.02 |
| F9 | 1.27 ± 0.01 |
| F10 | 1.28 ± 0.02 |
| Marketed Product | 1.27 ± 0.02 |

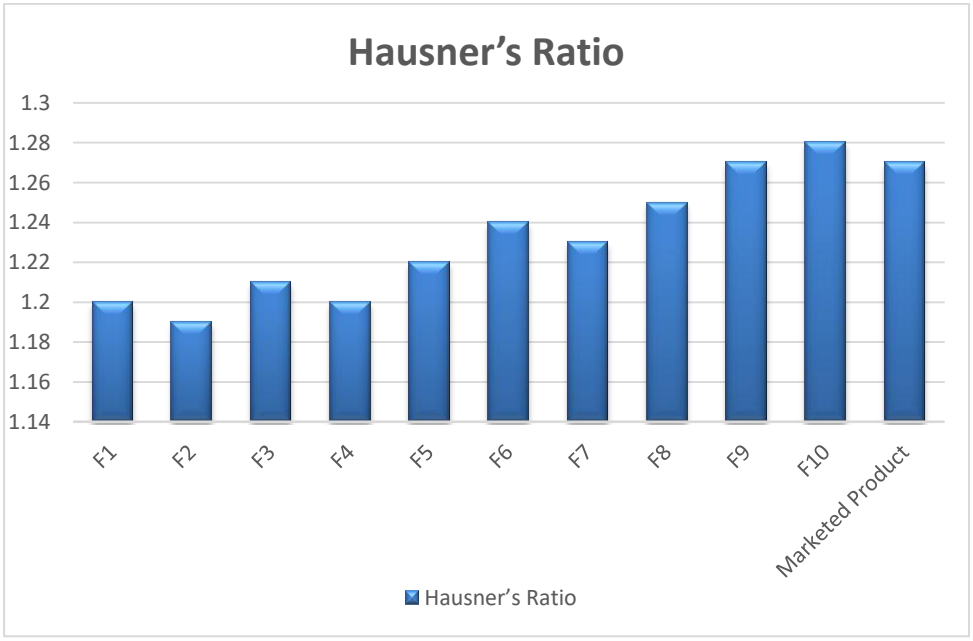


**Fig 5: Hausner's Ratio**

### 3.2.5 Angle of repose

The angle of repose of S-SNEDDS powder blends (F1–F10) ranged from 28.4 ± 0.6° to 38.2 ± 0.9°, indicating good to fair flow properties. Lower formulations (F1–F3) showed good flowability (<30°), while higher formulations (F8–F10) showed reduced flow (>35°) due to increased cohesiveness from higher SNEDDS loading. The marketed product (37.5 ± 0.8°) was comparable to higher formulations. Overall, all blends remained within acceptable limits for processing, with flowability decreasing as lipid content increased.

**Table 11: Angle of Repose of S-SNEDDS Powder Blend**

| Formulation Code | Angle of Repose (°) ± SD |
|---|---|
| F1 | 28.4 ± 0.6 |
| F2 | 29.1 ± 0.5 |
| F3 | 30.3 ± 0.7 |
| F4 | 31.0 ± 0.6 |

| | |
|---|---|
| F5 | 32.2 ± 0.5 |
| F6 | 33.5 ± 0.7 |
| F7 | 34.1 ± 0.6 |
| F8 | 35.6 ± 0.8 |
| F9 | 36.8 ± 0.7 |
| F10 | 38.2 ± 0.9 |
| Marketed Product | 37.5 ± 0.8 |

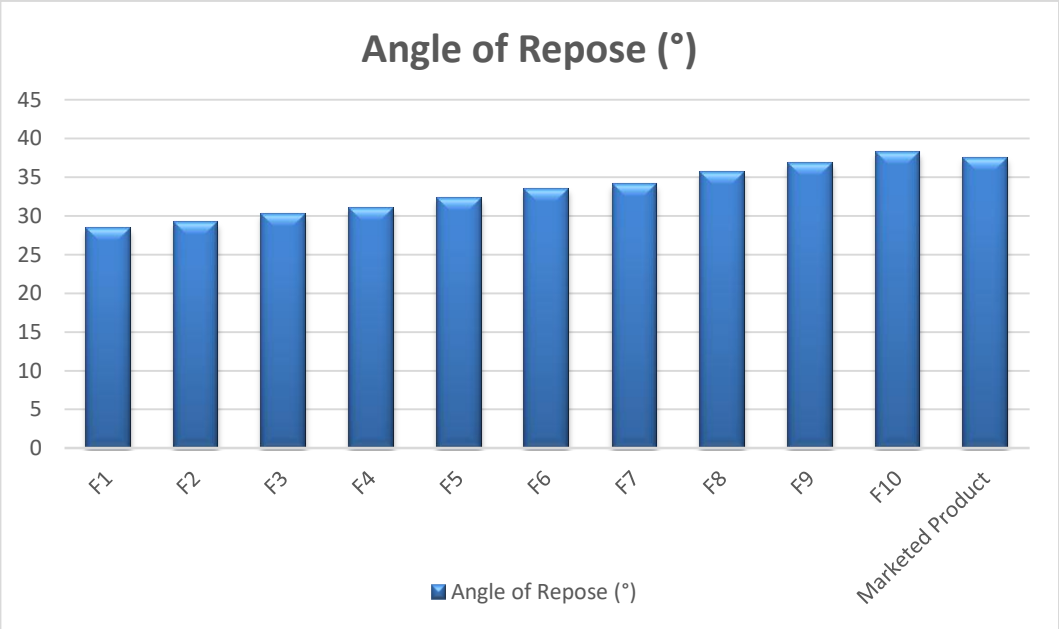


**Fig 6: Angle of Repose (°)**

### 3.3 Characterization of S-SNEDDS

#### 3.3.1 Physical appearance

The physical appearance of S-SNEDDS powder blends (F1–F10) showed variations with formulation composition. F1–F3 exhibited pale to light yellow, fine, smooth, and free-flowing powders with uniform appearance. F4–F5 remained uniform with slight increase in cohesiveness. From F6 onwards, a gradual shift to coarser texture and reduced flow was observed, with F8–F10 showing mild aggregation, darker coloration, and passable flow due to higher SNEDDS loading. The marketed product showed a uniform fine texture with good flow properties. Overall, lower to mid-range formulations showed better physical characteristics, while higher formulations showed slight reduction in flow behavior but remained suitable for further processing.

**Table 12: Physical Appearance of S-SNEDDS Powder Blend**

| Formulation Code | Color | Texture | Appearance | Flow Property |
|---|---|---|---|---|
| F1 | Pale yellow | Fine, smooth | Uniform, no aggregates | Free-flowing |
| F2 | Pale yellow | Fine, smooth | Uniform, no aggregates | Free-flowing |
| F3 | Light yellow | Fine, smooth | Uniform, no aggregates | Free-flowing |
| F4 | Light yellow | Smooth | Uniform, slight cohesiveness | Free-flowing |
| F5 | Light yellow | Smooth | Uniform, slight cohesiveness | Free-flowing |
| F6 | Yellow | Slightly coarse | Uniform, minimal lumps | Fair flowing |
| F7 | Yellow | Slightly coarse | Uniform, minimal lumps | Fair flowing |
| F8 | Yellow | Slightly coarse | Slight aggregation observed | Passable flow |
| F9 | Yellow | Coarse | Slight aggregation observed | Passable flow |
| F10 | Dark yellow | Coarse | Mild aggregation | Passable flow |
| Marketed Product | Yellow | Fine | Uniform, no aggregation | Good flow |

### 3.3.2 Homogeneity

The homogeneity of S-SNEDDS powder blends (F1–F10) was generally satisfactory, with most formulations showing uniform distribution across all sampled layers. F1–F7 exhibited excellent homogeneity, confirming efficient mixing and proper adsorption of liquid SNEDDS. Slight variations were observed in F8–F9 (top layer) and F10 (top and middle layers), likely due to higher SNEDDS loading causing minor segregation. However, no significant phase separation or aggregation was detected, and all formulations remained suitable for further processing. The marketed product also showed uniformity, confirming reliable drug distribution and dose consistency.

**Table 13: Homogeneity of S-SNEDDS Powder Blend**

| Formulation Code | Top Layer Observation | Middle Layer Observation | Bottom Layer Observation | Overall Homogeneity |
|---|---|---|---|---|
| F1 | Uniform | Uniform | Uniform | Homogeneous |
| F2 | Uniform | Uniform | Uniform | Homogeneous |
| F3 | Uniform | Uniform | Uniform | Homogeneous |
| F4 | Uniform | Uniform | Uniform | Homogeneous |
| F5 | Uniform | Uniform | Uniform | Homogeneous |
| F6 | Uniform | Uniform | Uniform | Homogeneous |
| F7 | Uniform | Uniform | Uniform | Homogeneous |
| F8 | Slight variation | Uniform | Uniform | Acceptable |
| F9 | Slight variation | Uniform | Uniform | Acceptable |
| F10 | Slight variation | Slight variation | Uniform | Acceptable |
| Marketed Product | Uniform | Uniform | Uniform | Homogeneous |

### 3.3.3 Polydispersity index (PDI) and Droplet size

The droplet size and PDI of reconstituted S-SNEDDS (F1–F10) showed improved nanoemulsion quality with increasing formulation ratio. Droplet size decreased from 182.4 ± 4.2 nm (F1) to 61.4 ± 1.8 nm (F10), indicating better emulsification and formation of finer droplets at higher SNEDDS levels. PDI also reduced from 0.312 ± 0.02 to 0.152 ± 0.01, showing improved uniformity and narrow size distribution. F8–F10 showed droplet sizes <80 nm with PDI <0.2, indicating excellent stability. Compared to the marketed product (95.6 ± 2.5 nm; PDI 0.220 ± 0.02), optimized formulations performed better. Overall, F10 showed the best nanoemulsion characteristics, supporting enhanced dissolution and bioavailability.

**Table 14: Droplet Size and Polydispersity Index (PDI) of Reconstituted S-SNEDDS**

| Formulation Code | Droplet Size (nm) ± SD | PDI ± SD |
|---|---|---|
| F1 | 182.4 ± 4.2 | 0.312 ± 0.02 |
| F2 | 165.8 ± 3.8 | 0.298 ± 0.01 |
| F3 | 148.6 ± 3.5 | 0.276 ± 0.02 |

| | | |
|---|---|---|
| F4 | 132.2 ± 3.1 | 0.254 ± 0.01 |
| F5 | 118.5 ± 2.9 | 0.231 ± 0.01 |
| F6 | 102.4 ± 2.6 | 0.214 ± 0.01 |
| F7 | 89.7 ± 2.3 | 0.198 ± 0.01 |
| F8 | 76.5 ± 2.1 | 0.182 ± 0.01 |
| F9 | 68.2 ± 1.9 | 0.168 ± 0.01 |
| F10 | 61.4 ± 1.8 | 0.152 ± 0.01 |
| Marketed Product | 95.6 ± 2.5 | 0.220 ± 0.02 |

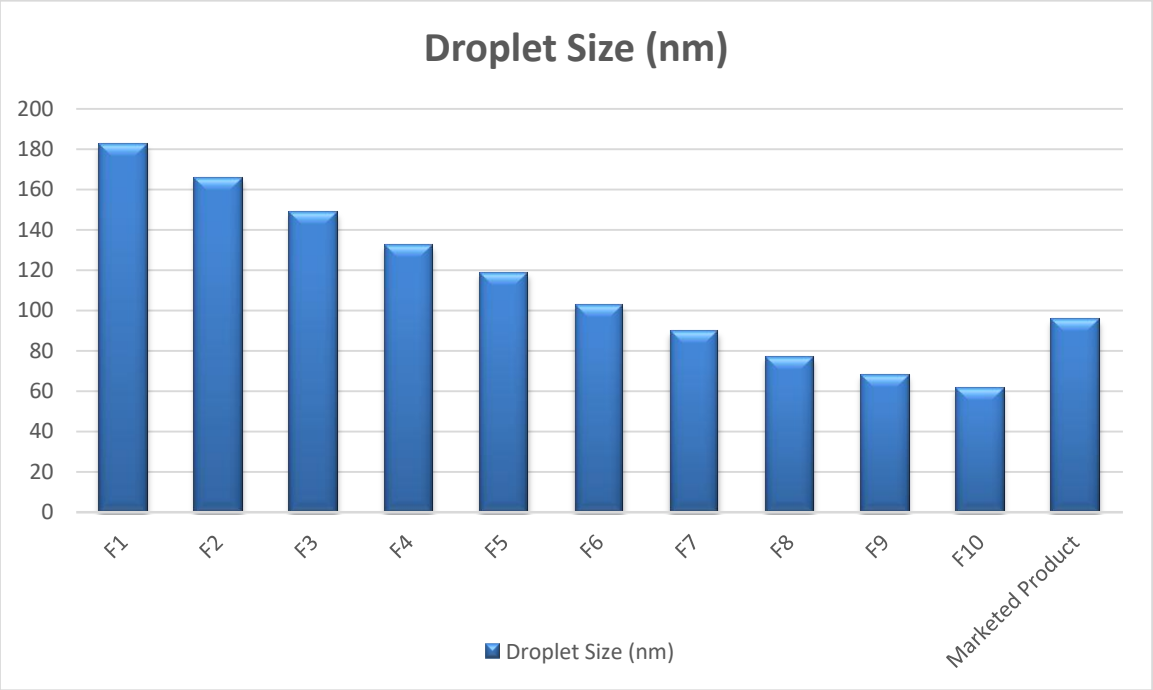


**Fig 7: Droplet Size (nm)**

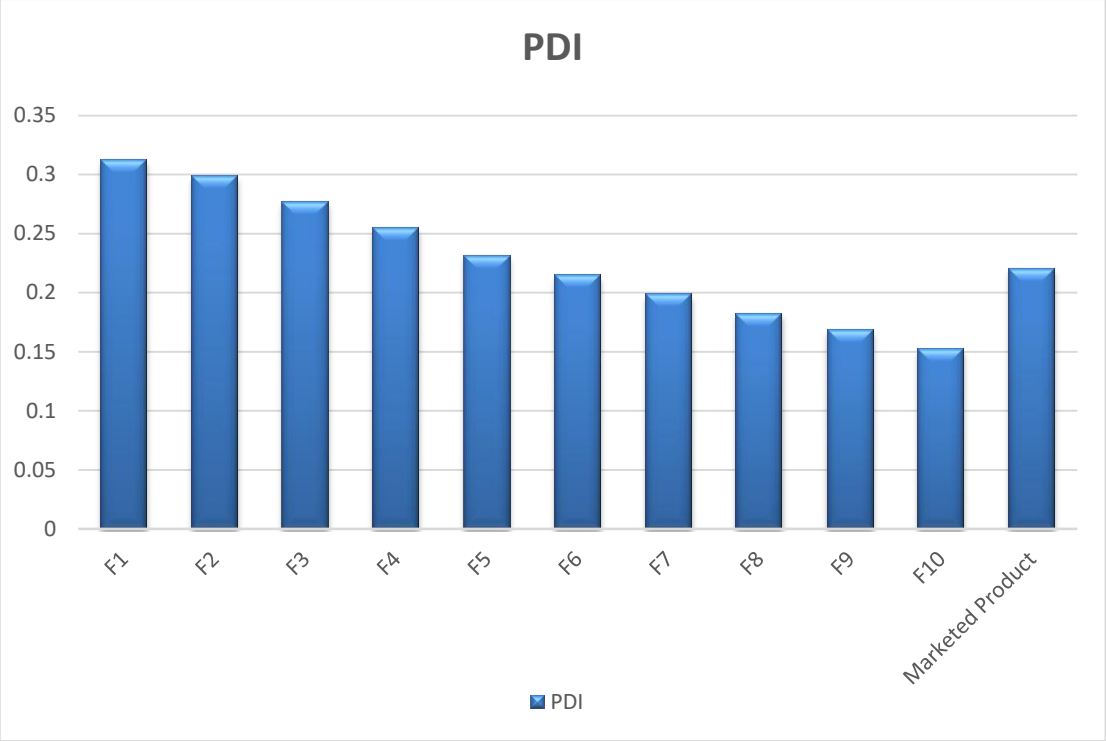


**Fig 8: PDI**

### 3.3.4 Zeta potential

The zeta potential of S-SNEDDS formulations (F1–F10) showed increasing negative surface charge from −12.4 to −36.4 mV with higher SNEDDS content, indicating improved electrostatic stability. F1 showed the lowest stability (−12.4 ± 0.8 mV), while F10 exhibited the highest magnitude (−36.4 ± 0.8 mV), suggesting strong repulsion and reduced risk of aggregation. The marketed product showed −25.1 ± 0.9 mV, which was lower than F10. Overall, F8–F10 demonstrated good colloidal stability, with F10 being the most stable formulation.

**Table 15: Zeta Potential of Reconstituted S-SNEDDS**

| Formulation Code | Zeta Potential (mV) ± SD |
|---|---|
| F1 | -12.4 ± 0.8 |
| F2 | -14.2 ± 0.7 |
| F3 | -16.8 ± 0.9 |
| F4 | -18.5 ± 0.8 |
| F5 | -21.3 ± 0.7 |
| F6 | -24.6 ± 0.9 |
| F7 | -27.2 ± 0.8 |
| F8 | -30.5 ± 0.7 |
| F9 | -33.8 ± 0.9 |
| F10 | -36.4 ± 0.8 |

| | |
|---|---|
| Marketed Product | -25.1 ± 0.9 |

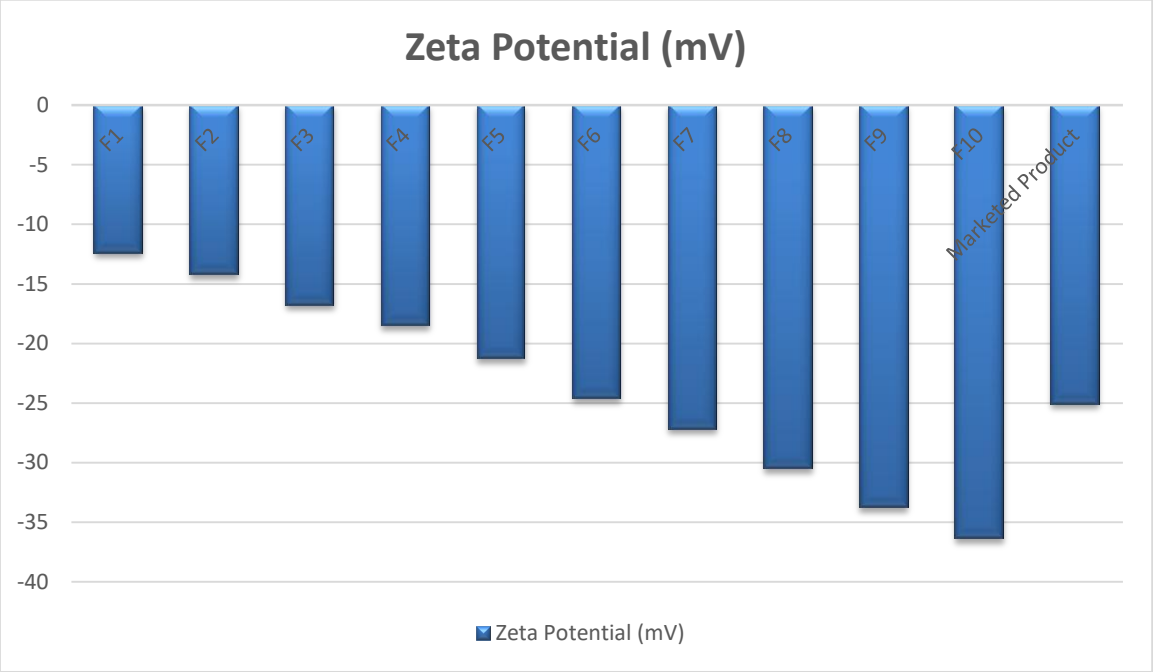


**Fig 9: Zeta Potential (mV)**

### 3.3.5 Drug content

The drug content of S-SNEDDS formulations (F1–F10) ranged from 96.2% to 99.5%, indicating uniform distribution of Pyronaridine with minimal loss during processing. Drug content increased up to F7 (99.5 ± 0.4%), suggesting efficient mixing and adsorption, followed by a slight decrease in higher formulations (F8–F10) due to increased loading effects. The marketed product showed 97.6 ± 0.7%. Overall, all formulations demonstrated good content uniformity and consistent dosing performance.

**Table 16: Drug Content of S-SNEDDS Formulations**

| Formulation Code | Drug Content (%) ± SD |
|---|---|
| F1 | 96.2 ± 0.8 |
| F2 | 97.1 ± 0.7 |
| F3 | 97.8 ± 0.6 |
| F4 | 98.4 ± 0.5 |
| F5 | 98.9 ± 0.6 |
| F6 | 99.2 ± 0.5 |
| F7 | 99.5 ± 0.4 |
| F8 | 99.1 ± 0.5 |
| F9 | 98.7 ± 0.6 |

| | |
|---|---|
| F10 | 98.3 ± 0.5 |
| Marketed Product | 97.6 ± 0.7 |

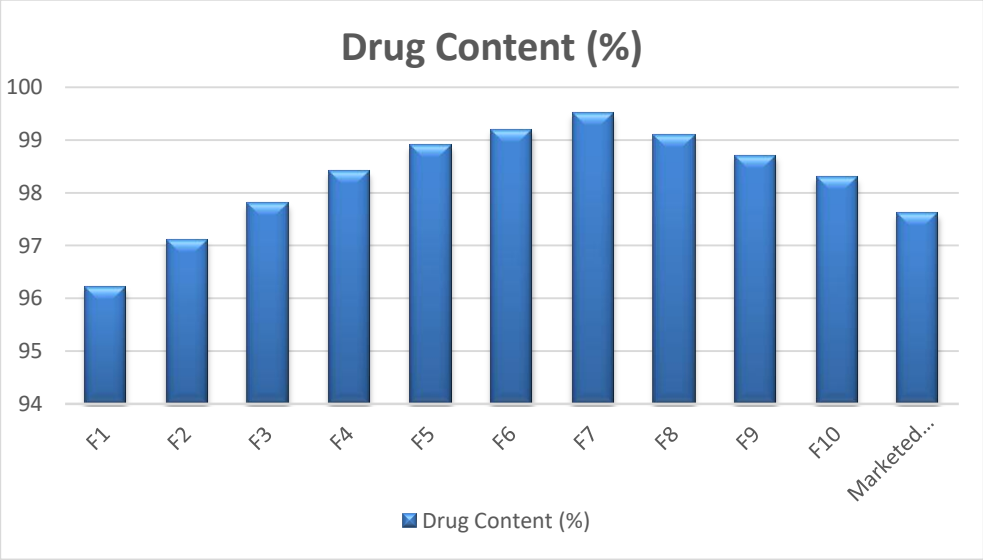


**Fig 10: Drug Content (%)**

### 3.3.6 Encapsulation efficiency

The encapsulation efficiency of S-SNEDDS formulations (F1–F10) ranged from 94.8% to 99.1%, indicating efficient incorporation of Pyronaridine into the lipid-based system with minimal drug loss. Efficiency increased up to F7 (99.1 ± 0.4%), suggesting optimal drug–excipient interaction, while a slight decline in F8–F10 was likely due to carrier saturation at higher loading levels. The marketed product showed 96.8 ± 0.7%, which was lower than the optimized batches. Overall, all formulations demonstrated excellent drug entrapment and reliable formulation performance.

**Table 17: Encapsulation Efficiency of S-SNEDDS Formulations**

| Formulation Code | Encapsulation Efficiency (%) ± SD |
|---|---|
| F1 | 94.8 ± 0.9 |
| F2 | 95.6 ± 0.8 |
| F3 | 96.4 ± 0.7 |
| F4 | 97.2 ± 0.6 |
| F5 | 97.9 ± 0.5 |
| F6 | 98.5 ± 0.5 |
| F7 | 99.1 ± 0.4 |
| F8 | 98.7 ± 0.5 |

| | |
|---|---|
| F9 | 98.2 ± 0.6 |
| F10 | 97.6 ± 0.5 |
| Marketed Product | 96.8 ± 0.7 |

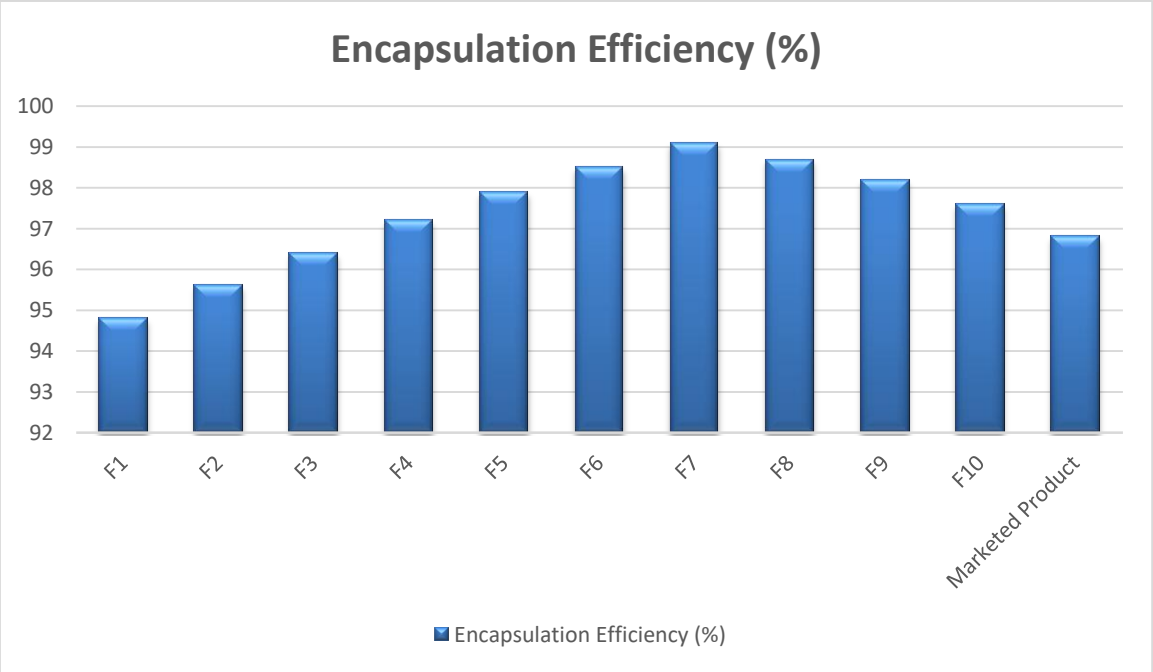


**Fig 11: Encapsulation Efficiency (%)**

### 3.4 In Vitro Dissolution Studies

The in vitro dissolution study showed significantly improved release of Pyronaridine from S-SNEDDS tablets compared to the marketed product. All formulations (F1–F10) exhibited time-dependent release, confirming effective self-emulsification and enhanced solubilization. Among them, F10 showed the fastest and most complete release, with 45.5% drug release at 5 minutes and 100% within 60 minutes. A progressive increase in release was observed from F1 to F10, indicating improved performance with higher SNEDDS content. Formulations F7–F10 released more than 95% drug within 45 minutes, whereas the marketed product showed slower release (22.4% at 5 minutes and 80.6% at 60 minutes). Overall, the enhanced dissolution is attributed to improved wetting, reduced interfacial tension, and nanoemulsion formation, suggesting better bioavailability potential.

**Table 18: In Vitro Drug Release Profile of S-SNEDDS Tablets**

| Formulation Code | 5 min (%) | 10 min (%) | 15 min (%) | 30 min (%) | 45 min (%) | 60 min (%) |
|---|---|---|---|---|---|---|
| F1 | 18.2 ± 0.8 | 28.6 ± 0.9 | 38.5 ± 1.0 | 52.4 ± 1.1 | 62.8 ± 1.2 | 70.2 ± 1.3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| F2 | 20.5 ± 0.7 | 32.4 ± 0.8 | 44.2 ± 0.9 | 58.6 ± 1.0 | 69.5 ± 1.1 | 76.8 ± 1.2 |
| F3 | 22.8 ± 0.7 | 36.8 ± 0.8 | 49.8 ± 0.9 | 65.2 ± 1.0 | 75.6 ± 1.1 | 82.5 ± 1.2 |
| F4 | 25.6 ± 0.6 | 40.5 ± 0.7 | 55.6 ± 0.8 | 71.8 ± 0.9 | 82.4 ± 1.0 | 88.7 ± 1.1 |
| F5 | 28.4 ± 0.6 | 45.2 ± 0.7 | 61.3 ± 0.8 | 78.5 ± 0.9 | 88.6 ± 1.0 | 93.2 ± 1.1 |
| F6 | 32.1 ± 0.5 | 50.6 ± 0.6 | 67.8 ± 0.7 | 84.6 ± 0.8 | 92.5 ± 0.9 | 96.4 ± 1.0 |
| F7 | 35.8 ± 0.5 | 55.4 ± 0.6 | 72.5 ± 0.7 | 88.2 ± 0.8 | 95.1 ± 0.9 | 98.2 ± 1.0 |
| F8 | 38.6 ± 0.5 | 60.2 ± 0.6 | 77.6 ± 0.7 | 91.5 ± 0.8 | 97.8 ± 0.9 | 99.4 ± 1.0 |
| F9 | 41.2 ± 0.5 | 64.8 ± 0.6 | 82.1 ± 0.7 | 94.2 ± 0.8 | 99.1 ± 0.9 | 99.8 ± 1.0 |
| F10 | 45.5 ± 0.5 | 69.3 ± 0.6 | 86.4 ± 0.7 | 97.1 ± 0.8 | 100.0 ± 1.0 | 99.8 ± 0.9 |
| Marketed Product | 22.4 ± 0.7 | 35.7 ± 0.8 | 48.2 ± 0.9 | 62.8 ± 1.0 | 72.4 ± 1.1 | 80.6 ± 1.2 |

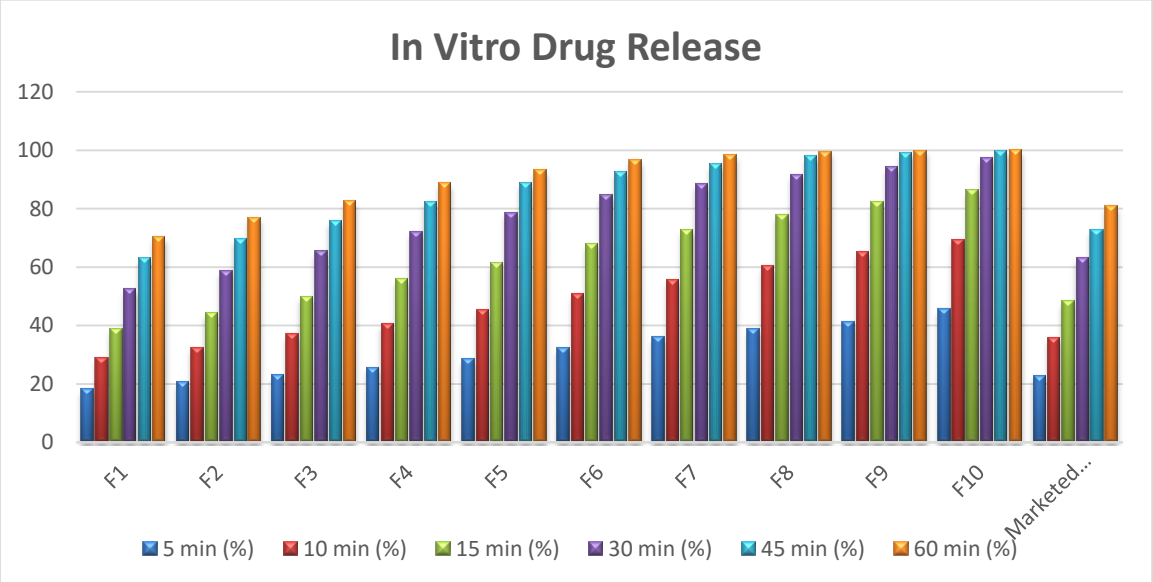


**Fig 12: In Vitro Drug Release**

### 3.5 Stability Studies as per ICH guidelines

The stability study of the optimized S-SNEDDS formulation (F10) showed good stability under both long-term (25 ± 2°C / 60 ± 5% RH) and accelerated (40 ± 2°C / 75 ± 5% RH) conditions over three months. No significant changes were observed in physical appearance, and the formulation remained uniform and free-flowing throughout storage. Drug content

showed only a slight decrease (98.3% to 97.5% under long-term conditions), while dissolution performance remained nearly unchanged (100% to 98.8% at 60 minutes). Under accelerated conditions, a minor moisture uptake was noted after two months, but without affecting integrity or performance. Drug content slightly decreased to 96.8%, and drug release remained above 97% at 60 minutes. Overall, the formulation demonstrated good physical and chemical stability, confirming its suitability for long-term storage and further development.

**Table 19: Stability Study of Optimized S-SNEDDS Formulation (F10) under ICH Conditions**

| Condition | Time Interval | Physical Appearance | Drug Content (%) ± SD | Drug Release at 60 min (%) ± SD |
|---|---|---|---|---|
| 25 ± 2°C / 60 ± 5% RH | 0 Month | Yellow, uniform | 98.3 ± 0.5 | 100.0 ± 0.0 |
| 25 ± 2°C / 60 ± 5% RH | 1 Month | No change | 98.1 ± 0.4 | 99.6 ± 0.2 |
| 25 ± 2°C / 60 ± 5% RH | 2 Months | No change | 97.8 ± 0.6 | 99.2 ± 0.3 |
| 25 ± 2°C / 60 ± 5% RH | 3 Months | No change | 97.5 ± 0.5 | 98.8 ± 0.4 |
| 40 ± 2°C / 75 ± 5% RH | 0 Month | Yellow, uniform | 98.3 ± 0.5 | 100.0 ± 0.0 |
| 40 ± 2°C / 75 ± 5% RH | 1 Month | No change | 97.9 ± 0.6 | 99.2 ± 0.3 |
| 40 ± 2°C / 75 ± 5% RH | 2 Months | Slight moisture | 97.2 ± 0.7 | 98.6 ± 0.4 |
| 40 ± 2°C / 75 ± 5% RH | 3 Months | Slight moisture | 96.8 ± 0.6 | 97.9 ± 0.5 |

## 4. Conclusion

In the present study, a solid self-nanoemulsifying drug delivery system (S-SNEDDS) of the antimalarial drug Pyronaridine was successfully developed and evaluated to enhance its solubility, dissolution, and potential oral bioavailability. Preformulation studies confirmed the drug's suitability for lipid-based delivery, showing poor aqueous solubility, moderate lipophilicity, and good compatibility with selected excipients. The optimized liquid SNEDDS exhibited rapid self-emulsification and stable nanoemulsion formation, which was effectively converted into a solid form using colloidal silicon dioxide without loss of performance. The developed S-SNEDDS showed satisfactory flow properties, uniform drug content, high encapsulation efficiency, and nanosized droplets with low polydispersity index upon reconstitution, indicating a stable and uniform system. The optimized formulation (F10) demonstrated superior in vitro drug release compared to the marketed product, achieving nearly complete release within 60 minutes due to enhanced wetting and reduced interfacial tension. Stability studies as per ICH guidelines further confirmed the formulation's robustness under both long-term and accelerated conditions with minimal changes in drug content and dissolution behavior. Overall, the developed S-SNEDDS of Pyronaridine proved to be a promising strategy for improving its biopharmaceutical performance and holds significant potential for further development toward enhanced oral antimalarial therapy.

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