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Formulation, Development, Characterization, and Cytotoxicity Study of Dasatinib Monohydrate Loaded Solid Self-Nano Emulsifying Drug Delivery System (SNEDDS) for Enhancement of Solubility and Oral Bioavailability

Kedar R. Bavaskar[a*], Ashkan I. Shaikh[b], Ashish S. Jain[c], Dilip O. Morani[d], Shrikant Joshi[e]

[a] *Assistant Professor, Department of Pharmaceutics, Shri D.D Vispute college of Pharmacy and Research Center, Vichumbe, Panvel – 410206, Maharashtra, India.*
[b] *Research Scholar, Department of Pharmaceutics, Shri D.D Vispute college of Pharmacy and Research Center, Vichumbe, Panvel - 410206, Maharashtra, India.*
[c] *Principal, Shri D.D Vispute college of Pharmacy and Research Center, Vichumbe, Panvel – 410206, Maharashtra, India.*
[d] *Assistant Professor, Bombay Institute of Pharmacy & Research, Dombivli (E), Mumbai – 421201, India.*
[e] *Associate Professor, Maliba Pharmacy College, Maliba campus, Gopal Vidyanagar, Bardoli, Surat, Gujarat - 394350, India.*

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Abstract

To improve the dissolution and solubility of dasatinib monohydrate (DAS), this study aimed to develop a solid self-nanoemulsifying drug delivery system (S-SNEDDS). Syloid 244FP was utilized as a solid carrier in this study to formulate and further develop liquid SNEDDS (L-SNEDDS) containing dasatinib monohydrate into a solid form. Based on the findings of the initial screening, nine batches of DAS-loaded SNEDDS were prepared using Tween 20, PEG 400, and Capryol 90 as surfactant, cosurfactant, and oil, respectively. Ternary phase diagrams were created for the chosen systems to determine the nanoemulsification region. The study demonstrates that the average globule size of the optimized batch of Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) fell within the nanometric scale, with optimal Polydispersity Index (PDI) values. All batches also demonstrated rapid emulsification time, high drug loading efficiency, and good optical clarity. The development of uniform, spherical droplets smaller than 100 nm was demonstrated by TEM analysis. Over 90% of the DAS was released in about 120 minutes, according to in vitro DAS release from SNEDDS formulae. The optimized SNEDDS formulation was selected for conversion into solid SNEDDS (S-SNEDDS) using suitable solid carriers. The synthesized S-SNEDDS formulae were assessed for drug content, cytotoxicity, FTIR, in vitro dissolution, and micromeritic properties. It was discovered that S-SNEDDS formulations exhibited excellent flow characteristics, significant drug release, and elevated drug content. The MTT assay results indicate that DAS-S-SNEDDS exhibits a dose-dependent cytotoxic effect against the HL60 (Human Leukemia) cell line. Compared with standard cytotoxic agents, DAS-S-SNEDDS exhibits a significant, potent effect against the HL60 (Human Leukemia) cell line. In vitro drug release studies demonstrated a marked enhancement in the dissolution rate of DAS. These findings indicate that DAS-S-SNEDDS may serve as an effective strategy to enhance the oral bioavailability and solubility of DAS.

Keywords: SNEDDS; Lipid-based drug delivery; Oral bioavailability; Nanoemulsion; Cytoxicity study; Solubility.

*** Corresponding Author**:
Kedar R. Bavaskar, Assistant Professor, Department of Pharmaceutics, Shri D.D Vispute college of Pharmacy and Research Center, Vichumbe, Panvel – 410206, Maharashtra, India. E-mail: kedar.bavaskar@gmail.com.

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1. Introduction

Although the oral route is the most convenient and effective for drug administration, it poses challenges for compounds with poor aqueous solubility. This problem affects about 40% of novel chemical entities, leading to limited bioavailability, irregular absorption, and inconsistent dosing [1]. The Biopharmaceutics Classification System (BCS) states that, due to their poor permeability or solubility, Class II and IV drugs have significant absorption problems. Furthermore, more than half of newly developed medications are lipophilic, which further reduces their water solubility and absorption [2].

Lipid-based formulations are becoming increasingly common because they can increase the oral bioavailability of drugs that aren't very soluble in water when taken with meals high in fat. With a focus on drug delivery systems that self-nanoemulsify, a variety of lipid-based delivery techniques, including suspensions, solutions, and emulsions, have been investigated. When SNEDDS come into contact with gastrointestinal (GI) fluids, they create fine oil-in-water nanoemulsions. The nano-size range and increased solubility result in a larger surface area for drug absorption, thereby enhancing oral bioavailability. Additionally, it offers improved enzymatic and chemical stability (**Figure 1**) [3-7].

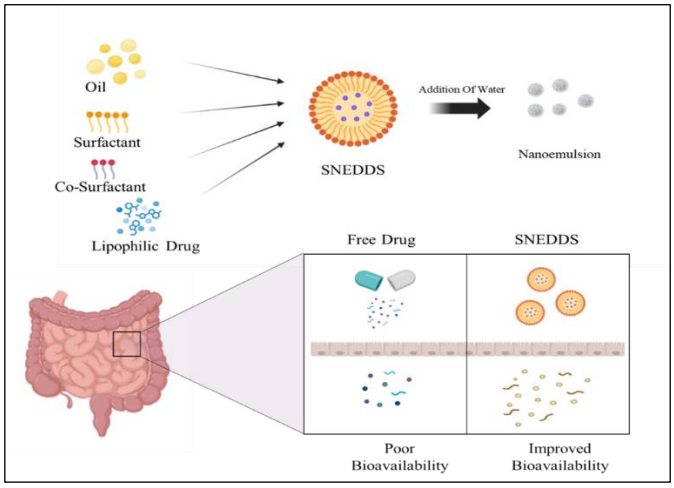

Figure 1. Mechanism of SNEDDS

Dasatinib Monohydrate (DAS) is a tyrosine kinase inhibitor [8]. In 2006, the FDA authorized its clinical use in both pediatric and adult patients. The agency has authorized indications for chronic myeloid leukemia (CML) Philadelphia chromosome-positive in the chronic phase, as well as for chromosome-positive acute lymphoblastic leukemia with resistance to prior therapies, including imatinib, and for accelerated, myeloid, chronic, or lymphoid blast phase Ph+ CML [9]. It is also regarded as a first-line treatment for CML [10, 11] and comes in different strengths as coated tablets. However, DAS has a relatively low oral bioavailability, ranging from 14% to 34% [12].

Furthermore, it was discovered that children's dispersed tablet bioavailability was 36% lower than that of intact tablets [9]. DAS is classified as BCS class II, which may explain its poor solubility (3.24 mg/mL) and high permeability (Log P = 3.83) in aqueous media, and consequently its low bioavailability. According to numerous reports, the dissolution and solubility of BCS class II medications affect their bioavailability [13]. Therefore, SNEDDS is a suitable approach to enhance its solubility and improve bioavailability.

2. Materials and methods

2.1. Materials

We received a sample of Dasatinib Monohydrate as a gift from Hetero Labs Limited in Hyderabad. Polyethylene glycol®400 (PEG 400), oleic acid, Propylene glycol, olive oil, linseed oil, aniseed oil, Tween®80, Tween®20, Span®20, Span®80, Span®60, and other materials were acquired from Research-Lab Fine Chem Industries, Mumbai, India. Gettefosse, Mumbai, Maharashtra, India, sent a gift sample of Capryol®90. The gift of Syloid®244 FP was from Grace Davison Chemicals (India) Pvt. Ltd., Kolkata, Kandanchavadi.

2.2. Methodology

2.2.1. Selection of self-nanoemulsifying drug delivery systems components

DAS Solubility in Various Surfactants, Cosurfactants, and Oils

Saturation solubility was tested on different oils (Olive Oil, Linseed Oil, Oleic acid, Capryol®90, Aniseed Oil), surfactants (Span®20, Tween®80, Tween®20, Span®80, Span®60), and co-surfactants (PEG®400, Propylene glycol) by adding some amount of drug to 3 ml of a selected component. The purpose was to determine which SNEDDS components had the greatest solubilizing capacity for DAS. To facilitate solubilization and achieve equilibrium, the drug samples in various vehicles were combined and stirred

continuously for 48 hours. Each sample was then centrifuged at 10,000 rpm for ten minutes. After that, the supernatant was collected and diluted with 10 mL of an appropriate solvent. A Shimadzu UV spectrophotometer set to 325 nm was used to measure the DAS concentration of the diluted samples [14]. The mean value (mg/mL) was used to characterize solubility, and each reading was performed in triplicate.

Surfactant (emulsification study)

Tween®80, Span®20, Tween®20, Span®80, and Span®60 were among the surfactants whose emulsification ability in the chosen oil was assessed. The selection process was based on the ease of emulsification and the transparency percentage [15]. After heating a 1:1 mixture of oil and surfactant to 50°C for 2 minutes, distilled water was added. The number of flask inversions required to produce a transparent nanoemulsion was recorded. Using a UV-Vis spectrophotometer, the emulsion's transmittance at 650 nm was measured after 2 hours of standing. The surfactant with the highest transmittance and fewer inversions was selected to form a clear emulsion [16].

Co-surfactant (emulsification study)

To further screen the various cosurfactants (PEG400, propylene glycol) for their emulsification efficiency, the chosen surfactant and oily phase were employed. 0.2 ml of cosurfactant, 0.4 ml of a chosen surfactant, and 0.6 ml of a chosen oil were combined and assessed as described for surfactant screening [17].

2.2.2. Development of the pseudo-ternary phase diagram

Capryol®90 (oil), PEG 400 (co-surfactant), and Tween®20 (surfactant) were chosen for SNEDDS formulation based on solubility and emulsification studies. To determine the optimal component concentrations, a pseudoternary phase diagram was constructed at 25°C using Various oil-to-Smix ratios (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1) and surfactant and co-surfactant (Smix) ratios (1:1, 1:2, 2:1, and 3:1) were assessed. CHEMIX school 12.5 software was used to analyze the ideal ratios, and the following combinations were gently stirred and titrated with water. For consistency, the studies were conducted three times. Furthermore, by incorporating DAS into the border formulations of the self-emulsifying domain and visually assessing performance following infinite dilution in purified water, the impact of DAS on self-emulsification was evaluated [18].

2.2.3. Preparation of DAS-Loaded L-SNEDDS

After identifying the self-nanoemulsifying area, SNEDDS formulations were developed with the appropriate component ratios. Pseudoternary phase diagrams were also used to optimize the surfactant-cosurfactant (Smix) ratio. Some SNEDDS batches were created using different weight ratios of Smix (40–60% v/v) and selected oil (10–30% v/v), as shown in **Table 1**. The DAS content remained constant across all formulas. In summary, a vortex mixer was used to thoroughly mix oil, surfactant, and cosurfactant in stoppered glass vials after they had been precisely weighed. The oil and Smix mixture was continuously stirred while a specific amount of DAS was added until the DAS was completely dissolved. In a water bath, these systems were heated to 40°C for 30 minutes while gently shaken to produce a clear solution. Before reuse, the prepared batches were kept at room temperature (**Figure 2**) [19].

Table 1. Formulation table of Dasatinib Monohydrate-loaded L-SNEDDS

Batch No.	DAS (mg)	Smix (% v/v)	Oil (% v/v)
F1	100	40	10
F2	100	50	10
F3	100	60	10
F4	100	40	20
F5	100	50	20
F6	100	60	20
F7	100	40	30
F8	100	50	30
F9	100	60	30

Figure 2. Prepared Batches of Dasatinib Monohydrate-loaded L-SNEDDS.

2.3. DAS Loaded L-SNEDDS Evaluations

2.3.1. Robustness to Dilution

To assess the formulation's stability upon dilution, the SNEDDS was diluted in various aqueous media mimicking in vivo conditions. The formulation was diluted at multiple fold levels (e.g., 50×, 100×, and 1000×) using PBS 6.8, D.W., and 0.1 N HCl. Each diluted sample was gently mixed and visually inspected for phase separation, turbidity, or precipitation over a specified period. The formulations were left at room temperature and observed over 24 hours for any physical changes, such as clarity and uniformity, to assess their stability upon dilution [20-22].

2.3.2. Studies of Thermodynamic Stability

The stability of the resulting SNEDDS formulations was investigated using centrifugation, heat-cool cycles, and freeze-thaw cycles. The formulations were stored for 48 hours at each of the six heat-cool cycle temperatures, which ranged from 4°C to 45°C. The formulations that did not exhibit cracking, creaming, or phase separation were subsequently centrifuged for 30 minutes at 3500 rpm. Only those who passed both tests underwent three freeze-thaw storage cycles, with temperatures alternating between -20°C and 25°C for 45 to 48 hours [23].

2.3.3. Evaluation of Self-Emulsification Efficiency

A USP dissolution apparatus type II was adopted to test the self-emulsification efficiency of SNEDDS (Erweka, DT 600, Heusenstamm, Germany). After adding 1 ml of each formula, 500 mL of D.W. (distilled water) at 38°C was stirred with a stainless steel paddle spinning at 50 rpm. The formulations were analyzed through optical inspection, focusing on their final appearance and emulsification rate, using a grading system to evaluate in vitro performance [24]:

Class A: An emulsion that forms quickly, usually in less than a minute, and is translucent or faintly bluish.

Class B: A rapidly creating bluish-white emulsion that is a little less clear than Grade A.

Class C: A fine, milky emulsion developed in 120 seconds.

Class D: A subdued, grayish emulsion with a greasy look that takes more than three min to emulsify.

Class E: A mixture that has either little or no emulsification and big oil droplets on the surface.

2.3.4. Self-Emulsification Time

At the start of the experiment, 300 mL of D.W. was stirred in a glass beaker using a magnetic stirrer set to 100 rpm and maintained at 38 °C. A set volume (1 mL) of each batch of formulation was added, and the emulsification time was determined by monitoring the final nanoemulsion characteristics and the disappearance of SNEDDS. The time required for the preconcentrate to dissolve into a uniform mixture was known as the emulsification time [25].

2.3.5. Droplet Size Analysis and Polydispersibility Index (PDI) Determination

The average globule size and polydispersity index (PDI) of the self-nanoemulsifying formulation were analyzed to assess the nanoemulsion's uniformity and stability. The predetermined amount of SNEDDS was diluted with distilled water to mimic gastrointestinal conditions and provide suitable measurement conditions. The resulting dispersion was measured by dynamic light scattering (DLS) using a particle size analyzer at room temperature. Measurements provided information on the homogeneity and size distribution of the emulsion droplets; the lower the PDI value, the more uniform the droplet population. Every analysis was repeated three times to confirm reproducibility and reliability of results.

2.3.6. Zeta Potential Determination

To determine the surface charge and predict the electrostatic stability of the nanoemulsion system, the zeta potential of the SNEDDS formulation was measured. A zeta potential analyzer (such as the Malvern Zetasizer Nano series) with electrophoretic light-scattering capabilities was used to analyze the diluted sample after it was transferred to a clear disposable zeta cell. To ensure uniformity, measurements were taken at room temperature, and each sample was assessed three times.

2.3.7. Transmission Electron Microscopy

The synthesized SNEDDS formulations globule dimensions and surface shape were investigated using Transmission Electron Microscopy (TEM). Following tenfold dilution of the SNEDDS samples with D.W., a

small amount of the resulting nanoemulsion was deposited onto a copper grid to create a thin film. The films were recorded on a TEM after air-drying and negative-staining with 2% phosphotungstic acid [26].

2.3.8. Drug Entrapment Efficiency

20 ml of an appropriate solvent was used to load the DAS-loaded SNEDDS formulation. 1 ml of the above dispersion was removed, diluted with the same sample, and centrifuged at 10,000 rpm. After extraction, the supernatant was filtered using a 0.45 µm filter and examined at 325 nm using a UV spectrophotometer. Equation's formula was used to determine the entrapment efficiency [27, 28].

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Amount of drug entrapped}}{\text{Amount of drug added}} \times 100$$

2.3.9. In-Vitro Drug Release Study

The in vitro drug release behavior of the medication from the L-SNEDDS dispersion was evaluated using a modified dialysis technique. Dialysis bag tubing (MWCO 12000–14,000) was immersed in the release medium for a whole day. The dialysis bag was sealed and soaked in 100 mL of release medium in a shaking water bath set at 38°C with agitation at 100 rpm after 1 mL of the freshly prepared L-SNEDDS formulation (equivalent to 10 mg of DAS) had been diluted. The drug release from 1 mL samples that were extracted at predefined intervals was measured using a UV spectrophotometer calibrated to 329 nm. To maintain sink conditions, 1 mL of new-release medium was added [29].

2.4. Preparation of DAS-Loaded L-SNEDDS into S-SNEDDS

By adsorbing onto a carrier, such as Syloid 244 FP, the improved L-SNEDDS formulation was transformed into a free-flowing, compressible powder. This conversion process involved adding the adsorbent material to a mortar and mixing it until a paste-like mass was formed. The mixture was then heated at 50 °C for 0.5 to 1 hour and flowed through a sieve (No. 120) to attain a free-flowing solid SNEDDS (S-SNEDDS). After solidification, the S-SNEDDS were evaluated through various physicochemical characterization techniques [30].

2.5. Evaluation of DAS Loaded S-SNEDDS

2.5.1. S-SNEDDS's Micromeritic Properties [31-35]

2.5.1.1. Angle of Repose (θ)

The funnel method was used to measure the angle of repose of S-SNEDDS. A funnel containing precisely weighed samples was raised to the point where it barely touched the top of the pile of S-SNEDDS powder. A cone was formed by allowing the powder to flow freely, and its diameter was measured. A formula below was then utilized to determine the angle of repose:

$$\tan \theta = h/r$$

where r is the heap's radius, while h is its height.

2.5.1.2. Bulk and Tapped Density

The bulk and tapped densities of the solid SNEDDS were determined to assess the packing behavior and flow characteristics of the formulation. A graduated measuring cylinder was carefully filled with a pre-weighed amount of the solid SNEDDS (usually 2–5 g) without compacting the material.

After that, the cylinder was mechanically tapped for a specified number of taps (usually 500–1250) or until the volume stabilized, using a tapped density device (such as a USP-compliant tap density tester).

2.5.1.3. Compressibility Index

Using the equation, Carr's index was computed. We performed each measurement in triplicate.

Carr's index (%) = [(Tapped Density – Bulk Density)/Tapped Density] x 100

2.5.2. Fourier-Transformed Infrared Spectroscopy (FTIR)

FTIR spectra of pure Dasatinib Monohydrate, the optimized L-SNEDDS, and the formulated optimized S-SNEDDS formulations were recorded using a Shimadzu FTIR spectrophotometer.

2.5.3. Drug Loading Efficiency

To determine the content of DAS, 1 mL of the prepared SNEDDS formulation containing 20 mg of DAS was diluted with a suitable solvent, and the mixture was thoroughly mixed in a volumetric flask by inverting or shaking the container three times. After appropriate

dilutions, samples were prepared in triplicate, absorbance was measured at 325 nm using a Shimadzu UV-Vis spectrophotometer, and the drug content of each formulation was determined from a previously established calibration curve.

2.5.4. Cytotoxicity study of S-SNEDDS

The National Center for Cell Sciences (NCCS), located in Pune, provided the HL-60 human leukemia cell line. The cells were grown in RPMI-1640 medium supplemented with 10% fetal bovine serum and incubated at 38°C in a humidified atmosphere with 5% CO_2 . For the assay, cells were seeded at 1×10^4 cells/mL and incubated for 24 hours before further experimentation. Subsequently, 70 µL of cell suspension (equivalent to 10^4 cells/well) was dispensed into 96-well tissue culture-grade microplates, This was followed by the addition of 100 µL of culture medium and 100 µL of test samples at concentrations ranging from 10 to 100 µg/mL. Control wells received 0.2% DMSO in PBS along with the cell suspension. Every treatment was carried out three times. To assess the proportion of viable cells after treatment and to ascertain baseline cell viability, control samples were included.

The medium was carefully removed after being incubated for 24 hours at 38°C and 5% CO_2 in a Thermo Scientific BB150 CO_2 incubator. The plates were then incubated for an additional 4 hours under the same conditions after 20 µL of MTT reagent (5 mg/mL in PBS) was added to each well. Under a microscope, formazan crystals, a sign of metabolically active (viable) cells, were seen to develop.

Following incubation, the medium was removed by aspiration, and 200 µL of DMSO was added to each well to dilute the formazan crystals. Aluminum foil was used to shield the plates from the light while they were incubated for ten minutes at 37°C. At 570 nm, absorbance was determined with a Benesphera E21 ELISA microplate reader. Every measurement was conducted three times [36-40].

2.5.5. In Vitro Drug Release Study

The previously outlined method for the L-SNEDDS Section was used to perform an in vitro drug release study of Dasatinib monohydrate using the optimal S-SNEDDS formulae.

3. Result and Discussion

3.1. Various Surfactants, Co-surfactants, and Oil Solubility in DAS

Dasatinib Monohydrate's solubility data in various components at 37°C are shown in **Figure 3.** A range of oils with varying degrees of saturation was used. Out of all the oils, Capryol® 90 had the highest DAS solubility (57.64±0.93 mg/ml), followed by oleic acid (48.78±1.05 mg/ml), olive oil (36.89±0.64 mg/ml), linseed oil (24.38±1.08 mg/ml), and aniseed oil (24.63±0.51 mg/ml). DAS was found to have an aqueous solubility of 3–24 mg/ml. These outcomes led to the choice of Capryol®90 as the oil phase. Their capacity to emulsify the oil was then used to choose the surfactant and cosurfactant.

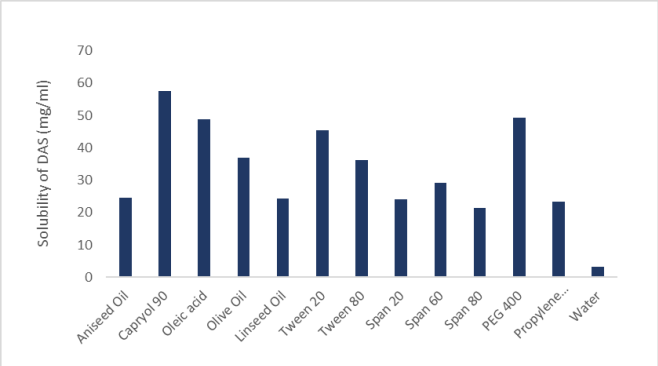

Figure 3. Solubility results data of Dasatinib Monohydrate in different components.

3.2. Selection of surfactant (emulsification study)

Generally accepted for oral consumption, nonionic surfactants are considered safer than ionic surfactants. The nonionic surfactants that were employed were Span®20, Span®80, Tween®80, Span®60, and Tween®20. The surfactants were evaluated based on their emulsification efficiency with the selected oil and their ability to solubilize DAS.

Based on the results data in **Table 2**, Tween 20 demonstrated the greatest potential in DAS solubilization and showed emulsion activity with the selected oil, Capryol®90. The %T of the resulting nanoemulsion will define the emulsification efficiency. Because Tween 20 and Tween 80 both provided transmittance above 90%, and considerable solubility of DAS was observed in these surfactants, these surfactants would be the focus of the experiments.

Table 2. Surfactant emulsification efficiency and DAS solubility in various nonionic surfactants.

Surfactants	HLB value	Solubility (mg/ml)	% Transmittance
Tween® 80	15.0	36.24±0.92	96.70±1.38
Tween® 20	16.7	45.36±1.05	98.23±0.92
Span® 20	8.6	24.12±0.80	76.01±0.81
Span® 80	4.3	21.30±1.06	53.57±2.84
Span® 60	4.7	29.21±0.89	65.12±2.43

Table 3. Effectiveness of emulsification when combining different co-surfactants with the selected surfactants.

Co-surfactants	Solubility (mg/ml)	% Transmittance	
		Tween® 20	Tween® 80
PEG 400	49.35	98.19±0.922	96.96±0.46
Propylene glycol	23.35	77.27±1.38	76.94±0.98

3.3. Selection of Co-surfactant (emulsification study)

The %transmittance of SNEDDS formulations with propylene glycol and PEG 400 as co-surfactants, Tween®80 or Tween®20 as surfactants, and Capryol®90 as the oil was measured. When combined with Tween®80, propylene glycol produced a lower % transmittance, whereas PEG®400 demonstrated the highest % transmittance. PEG®400 was chosen as the co-surfactant for additional research due to its exceptional DAS solubility and the highest transmittance (97–87 %), both of which were attributed to its ability to solubilize DAS and enhance nanoemulsification efficiency (**Table 3**).

3.4. Pseudo-Ternary Phase Diagram

A key characteristic of SNEDDS is that its properties change as the system is diluted, potentially leading to drug precipitation as the solvent capacity decreases. This was addressed by developing ternary phase diagrams to determine the self-nanoemulsifying region and the optimal surfactant, cosurfactant, and oil concentrations for SNEDDS formation. Phase diagrams were plotted at various surfactant to cosurfactant (Smix) ratios (1:1, 1:2, 2:1, and 3:1). The self-nanoemulsification efficiency increases with the size of the nanoemulsion zone in the diagram. As shown in **Figure 4**, formulations with a 1:2 ratio of the Tween®20-PEG 400 mixture (Smix) exhibited the largest emulsification zone, indicating that this ratio was optimal for stability, as indicated by the phase diagrams. The larger nanoemulsion region at this ratio could be due to increased fluidity at the interface and reduced interfacial tension.

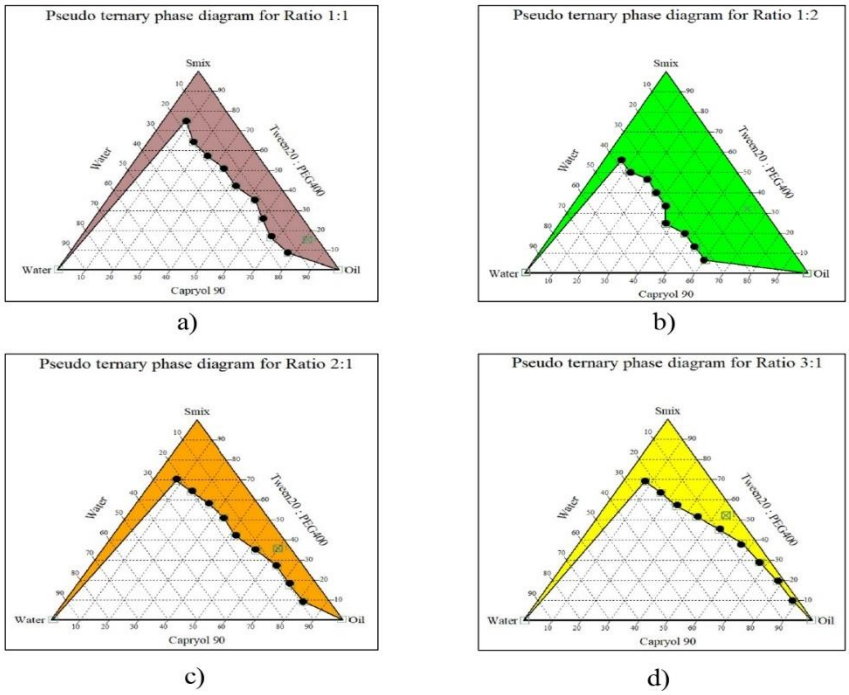

Figure 4. Pseudo-Ternary Phase Diagram of Smix Ratio (1:1, 1:2, 2:1, 3:1)

3.5. Characterization and Evaluation of DAS-Loaded L-SNEDDS

3.5.1. Studies of Thermodynamic Stability

After heat, centrifugation, and freeze-thaw cycles, all DAS-loaded SNEDDS batches showed no cloudiness, precipitation, or phase separation, indicating the stability of all reconstituted nanoemulsions. All of the formulae had the same physical appearance, as shown in **Table 4**, and visual assessment revealed no phase separation or flocculation. Therefore, under these stress conditions, it was determined that all SNEDDS formulae had acceptable overall stability.

Table 4. Studies of the thermodynamic Stability of all batches of DAS-L-SNEDDS.

Batches	Heat-Cool Cycles	Centrifugation Test	Freeze Thaw Cycles
F1	✓	✓	✓
F2	✓	✓	✓
F3	✓	✓	✓
F4	✓	✓	✓
F5	✓	✓	✓
F6	✓	✓	✓
F7	✓	✓	✓
F8	✓	✓	✓
F9	✓	✓	✓

Where (✓) indicates the batches passed the test.

3.5.2. Robustness to Dilution

To be employed as a drug delivery carrier, after dilution, SNEDDS must not undergo phase separation or drug precipitation. All SNEDDS batches were diluted, as shown in **Table 5**. illustrates, the resultant Batches F3, F4, F5, F6, and F8 were found to be transparent or clear, with no signs of phase separation even after a day. In oral administration, where they had a higher likelihood of traveling through the digestive system as emulsified oil droplets with no phase separation, this indicated the system's suitability.

3.5.3. Evaluation of Self-Emulsification Efficiency (Dispersibility Test)

The results of the visual evaluation of the formulae's in vitro performances using the previously described grading system are displayed in **Table 6**. Based on visual observations, SNEDDS batches F3, F4, F5, F6, and F8 were classified as class A.

3.5.4. Zeta potential determination and droplet size

Drug release and absorption are influenced by the emulsion's globule size, which is crucial for self-emulsification performance. The optimized formulation is the recommended option for additional research because it showed the smallest particle size (88.6 ± 0.92 nm). Furthermore, it was found that free fatty acids were responsible for the negative charge on the oil globules in SNEDDS, which is crucial for absorption. Good formulation stability was indicated by the optimized formulation's zeta potential of -23.2 mV, which falls within the acceptable range for nanosuspension stability (usually ±30 mV) (**Figure 5 and 6**).

Table 5. Robustness to DAS-L-SNEDDS dilution results.

Batches	Distilled Water			0.1N HCL			PBS 6.8		
	10	100	1000	10	100	1000	10	100	1000
F1	✓	×	×	✓	✓	×	✓	×	✓
F2	×	×	✓	✓	×	✓	×	×	×
F3	✓	✓	✓	✓	✓	✓	✓	✓	✓
F4	✓	✓	✓	✓	✓	✓	✓	✓	✓
F5	✓	✓	✓	✓	✓	✓	✓	✓	✓
F6	✓	✓	✓	✓	✓	✓	✓	✓	✓
F7	✓	×	×	✓	×	✓	×	✓	×
F8	✓	✓	✓	✓	✓	✓	✓	✓	✓
F9	×	×	✓	✓	×	✓	×	✓	×

Where (✓) means batches showed no phase separation, while (×) showed batch phase separation.

Table 6. Visual assessment of the dispersibility test for different DAS-L-SNEDDS formulations.

Batches	Observations	Class
F1	Slow emulsification	C
F2	Slow emulsification	C
F3	Rapidly forming clear emulsion	A
F4	Rapidly forming clear emulsion	A
F5	Rapidly forming clear emulsion	A
F6	Rapidly forming clear emulsion	A
F7	Slow emulsification	C
F8	Rapidly forming clear emulsion	A
F9	Slow emulsification	C

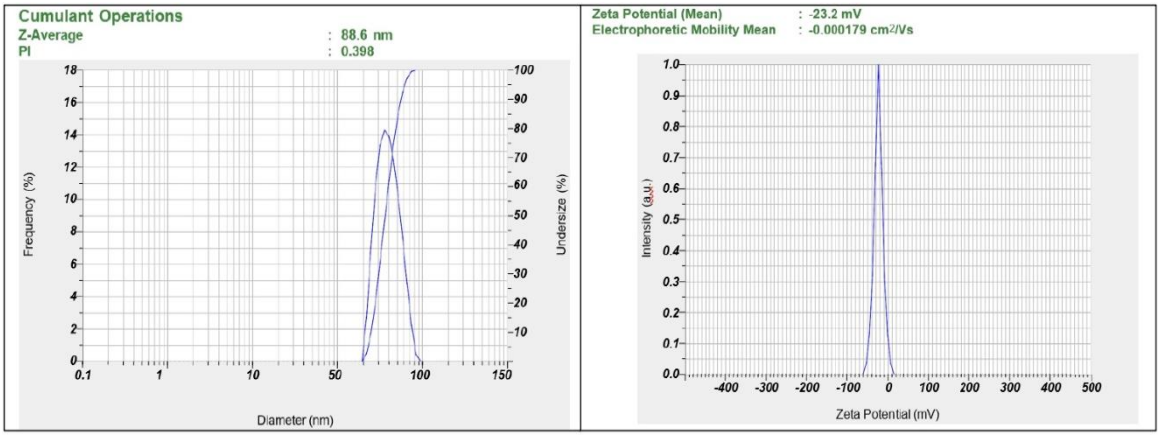

Figure 5. Particle size distribution and zeta potential of optimized Formulation.

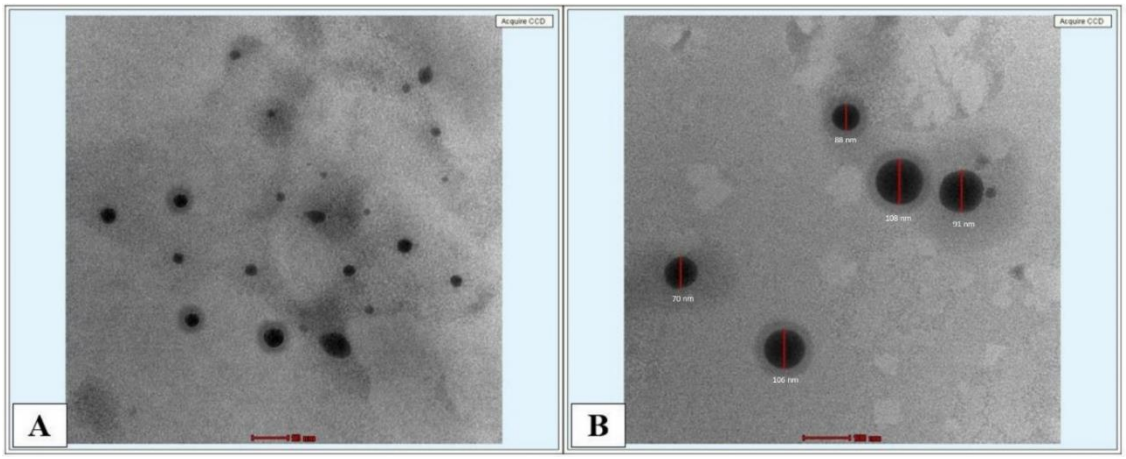

Figure 6. TEM images of Optimized formulation.

3.6. Preparation of DAS-Loaded L-SNEDDS into S-SNEDDS

One optimal L-SNEDDS batch was selected for conversion to S-SNEDDS after all conventional DAS-L-SNEDDS batches were ranked based on characterization and assessment tests. Batch F5 was selected as the optimal formulation for solidification based on thermodynamic stability investigations, resilience to dilution, drug entrapment efficiency, self-emulsification time, and % transmittance, as indicated in **Table 7** (**Figure 7**).

Figure 7. Solid form of SNEDDS formulation.

Table 7. Self-Emulsification Time, Drug Entrapment Efficiency and % Transmittance of various DAS-L-SNEDDS.

Batches	Self-Emulsification Time (s)	%T	Drug Entrapment Efficiency (%)
F1	68.73±0.9	89.67±0.47	81.22±0.2
F2	73.45±1.03	86.89±0.68	87.98±0.79
F3	57.64±1.21	91.65±0.46	89.37±0.26
F4	54.78±0.56	90.45±0.34	87.88±0.67
F5	46.79±0.57	97.89±0.68	92.01±0.82
F6	58.77±0.55	92.78±0.56	79.47±0.66
F7	67.89±0.68	82.35±0.24	87.31±0.22
F8	55.73±0.52	95.67±0.47	75.88±0.67
F9	69.88±0.67	83.44±0.33	71.39±0.28

3.7. Evaluation of DAS-Loaded S-SNEDDS

3.7.1. Micromeritic Properties of S-SNEDDS (**Table 8**)

3.7.2. Fourier Transformed Infrared Spectroscopy (FTIR)

The primary purpose of FTIR spectra is to ascertain how the drug interacts with any excipients that are used. The disappearance of the drug's key functional group indicates the presence of an interaction. The O–H group had a distinctive peak in the DAS IR spectrum at 3651 cm^{-1}, the C=O group had a peak at 1680 cm^{-1}, and the two C-N groups had a peak at 1184 cm^{-1}. Additionally, aromatic C-S stretching at 711 cm^{-1} and C-Cl stretching at 775 cm^{-1} were observed in the DAS spectrum. The prepared L-SNEDDS (F5 Batch) and prepared S-SNEDDS spectra showed similar peaks, and the absence of interfering peaks suggests that there are no undesired interactions, as seen in **Figure 8**.

Table 8. Micromeritic Properties of S-SNEDDS

Micromeritic Properties	Results
Angle of Repose	26.85°±0.62°
Bulk Density (g/mL)	0.45±0.04
Tapped Density (g/mL)	0.93±0.02
Carr's index (%)	13.25±0.204
Hausner's ratio	1.08±0.06

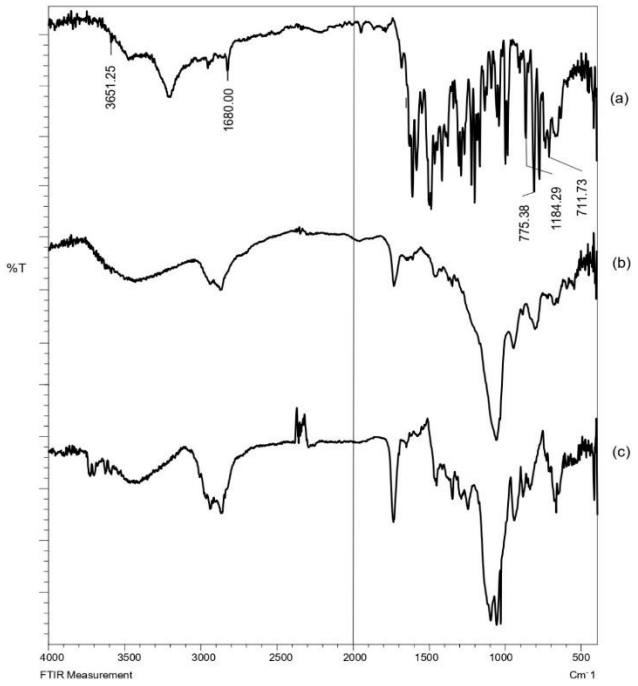

Figure 8. FTIR spectrum of a) Dasatinib Monohydrate b) L-SNEDDS (F5) c) S-SNEDDS.

3.7.3. Scanning Electron Microscopy (SEM)

A scanning electron microscope was used to determine the surface morphology of both pure DAS and DAS-S-SNEDDS, as illustrated in **Figure 9**. The DAS powder had an uneven crystalline shape, resembling needle-shaped crystals with rough surfaces. The size of its particles ranged widely, from less than 1µm to more than dozens of micrometers. However, the solid SNEDDS with DAS image shows that the particles shared the same outer macroscopic morphology, which was composed of evenly spaced spherical particles with comparable diameters and relatively deep dents. After being spray-dried, the crystalline DAS revealed itself to be extremely amorphous.

3.7.4. Drug Loading Efficiency

The S-SNEDDS's DAS content was found to be within the USP specification. The drug loading efficiency was determined to be 91.35 ± 0.24.

3.7.5. Cytotoxicity study of S-SNEDDS

The MTT assay results indicate that DAS-S-SNEDDS exhibits a dose-dependent cytotoxic effect against the HL60 (Human Leukemia) cell line. Cell viability decreases with increasing concentration, with values of 49.83% at 10 µg/ml, 43.75% at 40 µg/ml, and 30.6% at 100 µg/ml. Shown in **Figure 10** is the cytotoxic potential of DAS-S-SNEDDS.

The IC_{50} value (9.86 µg/ml) suggests cytotoxicity against HL-60 cells. Compared to other cytotoxic agents, DAS-S-SNEDDS exhibits a significant and highly potent effect against the HL60 (Human Leukemia) cell line [41] (**Table 9**).

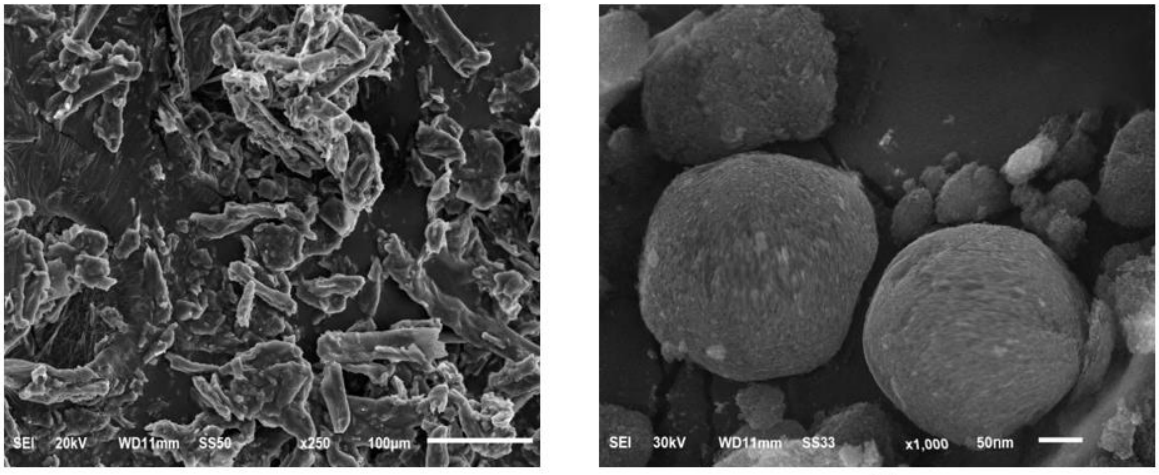

Figure 9. SEM photograph of a) Pure Dasatinib Monohydrate b) DAS-S-SNEDDS

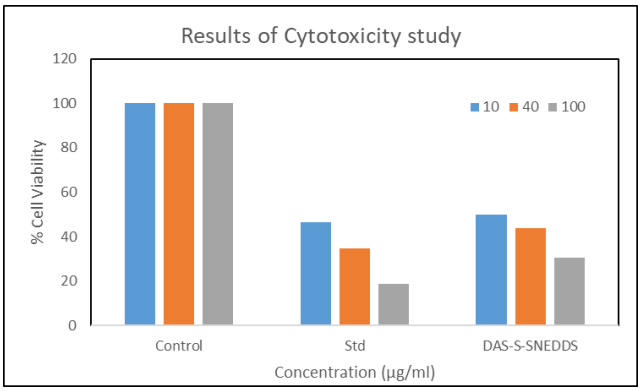

Figure 10. Graphical results of cytotoxicity study of S-SNEDDS.

Table 9. Effects of DAS- S-SNEDDS against the HL-60 cell line by MTT assay

Sr. No.	concentration (µg/ml)	Absorbance				Cell viability (%)	IC50 (µg/ml)
		1	2	3	Average		
1	Control	2.136	2.136	2.136	2.136		19.23
2	DAS-S-SNEDDS 10	1.065	1.066	1.064	1.065	49.83	9.86 µg/ml
3	40	0.935	0.945	0.925	0.935	43.75	
4	100	0.654	0.651	0.657	0.654	30.6	

3.7.6. In Vitro Drug Release Studies

The percentage DAS releasef rom S-SNEDDS was observed to be greater compared to both DAS-L-SNEDDS and pure DAS, as shown in **Figure 11**. Only 84.52±0.75 % and 22.09±0.46 % of DAS were released from DAS-L-SNEDDS and pure DAS during the first two hours of the in vitro drug release study. In contrast, the S-SNEDDS batch demonstrated better release during the same time frame. Within two hours, 91.44±0.93% of the DAS released and dissolved from S-SNEDDS had been achieved.

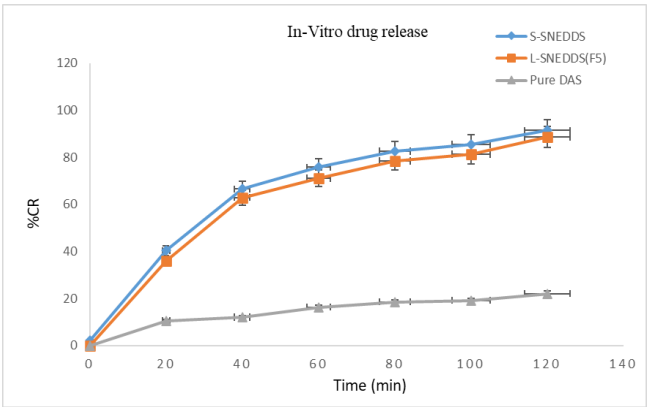

Figure 11. In-Vitro Drug Release of S-SNEDDS, L-SNEDDS, and Pure Drug.

3.8. Discussion

Dasatinib Monohydrate (DAS) S-SNEDDS was successfully developed and characterized in this study to improve its solubility, stability, and therapeutic efficacy. The development process was methodically directed by in vitro performance tests, thermodynamic stability assessments, emulsification evaluations, and solubility studies.

According to solubility screening, Capryol® 90 had the highest solubility in DAS (57.64±0.93 mg/ml), far outperforming other oils, such as olive oil and oleic acid. This significant increase in solubility is explained by Capryol® 90's amphiphilic properties, which facilitate the dissolution of hydrophobic medications such as DAS. On the other hand, DAS's aqueous solubility was significantly lower (3–24 mg/mL), underscoring the need for lipid-based delivery systems such as SNEDDS.

Based on its ability to solubilize drugs and emulsify, Tween®20 was found to be the most effective surfactant. The high transmittance values (>90 percent) of Tween 20 and Tween 80, which show good emulsification when combined with Capryol® 90, supported their selection. Among the co-surfactants tested, PEG®400 was found

to enhance emulsification synergistically, especially when combined with Tween 20, resulting in the highest transmittance (97–87%).

The formulation was further optimized using a pseudo-ternary phase diagram, which revealed that the optimal Smix ratio of 1:2 (Tween 20:PEG 400) produced the largest nanoemulsion region. This result highlights the crucial role of the surfactant- co-surfactant balance in lowering interfacial tension and promoting spontaneous emulsification.

The robustness of the DAS-loaded SNEDDS formulations was validated through thermodynamic stability studies, which showed no signs of instability, precipitation, or phase separation following stress testing. Additionally, the formulations showed outstanding dilution robustness. They retained clarity in the absence of precipitation, suggesting that they are appropriate for oral administration and the physiological dilution conditions of the gastrointestinal tract.

Batch F5 was chosen as the optimal formulation due to its exceptional performance across multiple parameters, including drug entrapment efficiency (92.01 ± 0.82), high %transmittance, droplet size (88.6 ± 0.92 nm), and thermodynamic stability. The possibility of particle aggregation was decreased by the zeta potential of -23.2 mV, which also validated acceptable physical stability.

Optimized L-SNEDDS were solidified into S-SNEDDS, which improved handling and storage stability while maintaining the formulation's desired properties. Good flow characteristics (Angle of repose: 26.85°, Carr's Index: 13.25 percent, Hausner's ratio: 1.08) were found by micromeritic analysis of the S-SNEDDS. These characteristics are critical for possible manufacturing and scale-up.

As FTIR analysis revealed no discernible drug-excipient interactions, DAS's chemical integrity within the S-SNEDDS matrix was guaranteed. According to USP standards, the drug loading efficiency was high (91.35±0.24%), demonstrating the formulation's capacity to deliver a therapeutically relevant dose of the drug.

The SEM analysis revealed distinct morphological differences between pure DAS and the DAS-loaded solid SNEDDS. Pure DAS showed irregular, needle-like crystalline structures with rough surfaces and a wide particle size distribution, reflecting its crystalline nature and poor dissolution potential. In contrast, the spray-dried solid SNEDDS displayed uniformly distributed spherical particles with surface dents, indicating solvent evaporation during drying. The absence of crystalline features confirmed that DAS had transformed into an amorphous form, suggesting improved solubility and dissolution, thereby supporting the potential of S-SNEDDS to enhance DAS bioavailability.

The cytotoxicity studies revealed that DAS-S-SNEDDS exhibited potent, dose-dependent cytotoxicity against HL60 leukemia cells, with an IC_{50} of 9.86 µg/mL. These findings suggest that the nanoemulsifying system not only enhances solubility and delivery but also potentially improves the pharmacological efficacy of DAS.

In vitro drug-release studies provided additional evidence of the S-SNEDDS formulation's superiority. The enhanced dissolution profile of S-SNEDDS was confirmed by a significantly higher release (91.44%) than that of pure DAS and DAS-L-SNEDDS, which only released 22.09% and 84.52%, respectively, in two hours. Increased surface area, smaller droplets, and the formulation's self-emulsifying properties may all contribute to the better release.

4. Conclusion

This study used Syloid 244FP as the solid carrier to formulate liquid SNEDDS and further develop them into solid SNEDDS. The formulated liquid SNEDDS was found to be thermodynamically stable, to have nanometric globule sizes, and to exhibit self-emulsification efficiency, suggesting physiological stability. Additionally, it was determined that DAS-S-SNEDDS exhibits a higher in vitro dissolution rate than L-SNEDDS and pure DAS and has a significant, potent effect against the HL60 (Human Leukemia) cell line compared to standard cytotoxic agents. Additionally, our findings indicate that S-SNEDDS may be considered and that they were further evaluated for their potential in the oral delivery of poorly soluble lipophilic drugs, particularly when oral administration is preferred. Overall, self-emulsifying drug delivery systems (SEDDS) represent an effective strategy for formulating such drugs. S-SNEDDS emerged as a promising solution

to the challenges of oral DAS administration, offering an innovative, commercially viable alternative to existing formulations. In summary, S-SNEDDS have demonstrated significant enhancement in the oral bioavailability of hydrophobic drugs, supporting their utility in improving oral drug delivery.

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Conflict of interest

The authors report there are no competing interests to declare

Data availability

The datasets from this study are available from the corresponding author upon reasonable request.

Authors Contributions

Study conception and design: Kedar Bavaskar, Formulation and experimental work: Ashkan Shaikh, Kedar Bavaskar, Data analysis and interpretation: Kedar Bavaskar, Drafting and revising the manuscript: Dilip Morani, Ashkan Shaikh, Final approval of the manuscript: Ashish Jain, Shrikant Joshi.

Authors Orcid numbers:

Kedar R. Bavaskar: 0009-0001-5575-3435
Ashkan I. Shaikh: 0009-0006-5874-1591
Ashish S. Jain: 0009-0001-6163-5363
Dilip O. Morani: 0000-0002-0820-6033
Shrikant Joshi: 0000-0001-9889-0571

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Using artificial intelligence chatbots

There was no use of artificial intelligence in the making of this article.

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