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Solid Self-Emulsifying Drug Delivery System (S-SEDDS) for Alpha-Lipoic Acid: A Novel Strategy to Enhance Solubility, Stability and Oral Bioavailability

Ketaki Phadke*, Gita Chaurasia, Swati Deshmukh

Siddhant College of Pharmacy's, Talegaon-Chakan Road, A/P-Sudumbare, Taluka Maval, Pune - 412109

Abstract

Alpha-lipoic acid (ALA) is a potent antioxidant with therapeutic potential in diabetic neuropathy, liver diseases, and neurodegenerative disorders. However, its clinical application is limited by poor water solubility and chemical instability, leading to reduced oral bioavailability. Initial studies revealed significant degradation of ALA approximately 30% under thermal stress and 17% in simulated gastric fluid (pH 1.2) and only 60% drug release in dissolution tests, underscoring its sensitivity to heat, acid and poor dissolution. To overcome these challenges, a Solid Self-Emulsifying Drug Delivery System (S-SEDDS) was developed using Medium-Chain Triglyceride (MCT) oil as the lipid phase, Cremophor RH 40 as surfactant, PEG 400 as co-surfactant and Neusilin UFL2 as the solid carrier. This formulation forms nanoemulsions upon contact with gastrointestinal fluids, enhancing solubility, stability and absorption. The optimized S-SEDDS demonstrated a significant increase in drug release, reaching 95.13% dissolution compared to 60% for pure ALA. Scanning Electron Microscopy (SEM) showed smooth, uniform particles, while Differential Scanning Calorimetry (DSC) confirmed conversion of crystalline ALA to an amorphous form, improving solubility. Drug content analysis confirmed 100% assay, indicating uniformity and stability. Stability studies under accelerated and ambient conditions over one month showed no significant changes in appearance, drug content or dissolution profile. These findings highlight S-SEDDS as a promising platform to enhance the delivery and therapeutic efficacy of ALA and other poorly soluble, unstable drugs.

Keywords: Alpha-lipoic acid; S-SEDDS; oral bioavailability; antioxidant; thermal instability; Neusilin UFL2; self-emulsifying drug delivery; amorphous conversion

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*Corresponding author

1. Introduction

Alpha-lipoic acid, al so-called alpha-lactic acid or thioic acid, is a constituent of organosulfur produced by humans, animals and plants. ALA is a small molecule with two oxidized and two reduced thiol groups. It has many advantages, including excellent antioxidant potential and widespread use as a racemic medicinal product in the treatment of pain associated with diabetic polyneuropathy and paresthesia. (1) ALA also serves as a cofactor for enzyme complexes involved in metabolic processes and in the production of cells. The reduced form of Lapp lactate is called Dihydrolipoic Acid (DHLA), while the oxidised form is usually called alpha-lipoic acid or simply lipoic acid. (2) Although DHLA is the most common form of the Reactive Oxygen Species (ROS) species, free radicals may also be inactive in the oxidized form of LA. Alpha-lipoic acid has shown potential benefits in managing various diseases, including Alzheimer's disease, diabetes and liver disorders. (3) Alpha-lipoic acid has demonstrated potential advantages in the management of various conditions, such as Alzheimer's disease, diabetes and liver disorders. (4-6) The ALA and DHLA pair form a strong redox couple with a standard reduction potential of −0.32 V. DHLA, in particular, can regenerate other natural antioxidants such as vitamins E and C, while also neutralizing free radicals. Both ALA and DHLA are effective at preventing the formation of protein carbonyls by scavenging hypochlorite. (7) However, the use of ALA is limited by its poor water solubility and its susceptibility to oxidation and thermal degradation. The distorted five-membered dithiolane ring structure of ALA may promote its polymerization, especially during thermal processing at temperatures above its melting point of 48–50°C. ALA undergoes polymerization and oxidative degradation, resulting in decreased bioactivity and the formation of an

undesirable sulfur-like odor. The elimination rate of ALA is characterized by a biological half-life of less than 30 minutes. (8) Alpha-lipoic acid is also unstable when subjected to low pH, light, or heat. ALA gradually decomposes at room temperature and readily polymerizes at temperatures above its melting point, which ranges from 46 to 49 °C. Consequently, the stabilization of RALA is of significant interest for industrial applications, and numerous studies have been conducted to stabilize ALA. (9) To address these challenges, various strategies have been employed, including cyclodextrin inclusion complexes, nano lipid carrier systems and enteric-coated tablets. Recently, SEDDS have become popular for improving the solubility of lipophilic drugs. (10) These systems come in both liquid (L-SEDDs) and solid (S-SEDDs) forms. Solid SEDDS are thought to provide better stability, consistent performance and greater patient compliance, along with easier process control. (11) By keeping the drug in a solubilized form and finely dispersed as droplets throughout its passage in the gastrointestinal tract, SEDDS efficiently improve the solubility of poorly soluble drugs, thereby increasing their bioavailability. (12) SEDDS can enhance the oral bioavailability of poorly water-soluble drug, but they face limitations such as stability, manufacturing challenges, interactions with capsule shells and sensitivity to storage temperature. At low temperatures, active ingredients or excipients may precipitate and must redissolve at room temperature to remain effective. Additionally, SEDDS require a moist environment for optimal performance. Solid SEDDS may help address these issues. (13)

Unlike traditional solubilization methods, the SEDDS approach offers the potential for synergistically enhancing the oral absorption of ALA by improving both its solubility and stability. Given these advantages, the application of S-SEDDS for delivering ALA could represent a promising strategy to enhance its nutraceutical efficacy. However, there is limited information available on its practical application. This study represents the first effort to develop a solid SEDDS formulation containing ALA (ALA/S-SEDDS) with the goal of enhancing its solubility and stability, especially under acidic conditions such as those present in the stomach. (14-15)

The present work describes an ALA(S-SEDDS) formulation was designed to improve the physicochemical and pharmacokinetic characteristics of ALA. The formulation was developed by combining RLA with optimized ratios of oil, surfactant and co-surfactant, chosen based on RLA's solubility in different excipients and informed by a pseudo-ternary phase diagram. The optimized ALA(S-SEDDS) was then assessed for its physicochemical attributes, including morphological characteristics, dissolution profile and stability in simulated gastric fluid (SGF). Additionally, the pharmacokinetics of ALA, were investigated following oral administration of ALA and the ALA/S-SEDDS formulation in rats.

2. Materials and Method

2.1 Materials

Alpha Lipoic Acid (active pharmaceutical ingredient, antioxidant), Medium Chain Triglyceride – MCT (oil), Cremophor RH 40 (surfactant), Tween 20 and Tween 80 (surfactants, emulsifiers), Span 20 (surfactant), PEG 40 (polyethylene glycol; co-surfactant), Propylene Glycol (co-surfactant), Glycerine (co-surfactant), Olive oil and Sunflower oil (alternative lipid phases), Neusilin UFL2 (adsorbent, solid carrier) were all received as gift samples from Zuventus Healthcare Ltd. All materials were of pharmaceutical grade.

2.2 Forced degradation study

Studies on forced degradation were carried out to assess the stability of Alpha Lipoic Acid (ALA) under various stress conditions in accordance with ICH guidelines. The primary objective was to identify the drug's sensitivity to environmental factors such as heat, pH, oxidation, hydrolysis and humidity. These studies help determine potential degradation pathways and provide essential information for the development of a robust and stable dosage form. (16) (Table 1)

Table 1. Forced Degradation Conditions Applied to Alpha Lipoic Acid

Sample Set	Purpose	Condition
Acidic Degradation	Assess stability in acidic environment (e.g., stomach)	pH 1.2 using HCl, 60°C heating for 1 hr
Alkali Degradation	Evaluate degradation in basic conditions (e.g., intestine)	pH 6.8 phosphate buffer, 60°C heating for 1 hr
Thermal Degradation	Test stability under heat	Heating at 50°C for 24 hr
Oxidative Degradation	Assess oxidation susceptibility	3% H_2O_2, heat at 60°C for 1 hr
Hydrolytic Degradation	General hydrolytic stability	Water, heat at 60°C for 1 hr
Humidity Degradation	Test moisture impact	40°C / 75% RH for 24 hr

2.3 FT-IR Spectral Analysis

Infrared Spectroscopy (FTIR) was utilized to analyze physical combinations of the drug with specific excipients, prepared in a 1:1 ratio, using an FTIR spectrophotometer (Shimadzu). The samples were scanned over the range of 4000–400 cm^{-1} using the KBr pellet method to evaluate the compatibility of Alpha Lipoic Acid with the selected excipients. The spectra from the mixtures were compared to that of the pure drug to identify any shifts, loss, or emergence of new peaks, suggesting potential interactions. (17)

2.4 Solubility study

This research aimed to identify oils, surfactants, and cosurfactants with the highest solubilizing capacity for Alpha lipoic acid. Excess drug was added to 1 ml of solvent in vials, shaken for 48–72 hours to form a slurry, then centrifuged at 4500 rpm for 10 minutes. The supernatant was filtered, diluted with water and analyzed

by UV spectrophotometry at 333 nm to measure drug content. These solubility results guided the selection of suitable components. (18-21)

3. Preparation of S-SEDDS

The pharmaceutical compound is dissolved in a blend of surfactant and co-surfactant. Pre-measured oil is incorporated into this blend while stirring with a magnetic stirrer to guarantee thorough mixing. This research focuses on identifying different oils, surfactants and cosurfactants that exhibit the highest solubilizing capacity for Alpha lipoic acid. The procedure involves adding an excess amount of the drug to 1 mL of solvent in vials. These vials are then agitated in an orbital shaker for 48–72 hours to achieve a uniform slurry. After agitation, the samples are centrifuged at 4500 rpm for 10 minutes to separate the supernatant, which is subsequently filtered using a syringe filter. The resulting filtrate is diluted with water and analyzed at 333 nm using a UV spectrophotometer to determine the drug concentration. These solubility studies form the basis for selecting the most suitable oil, surfactant, and co-surfactant. (22-24)

3.1 Evaluation of S-SEDDS (Capsule)

The formulated S-SEDDS capsules were then evaluated for various parameters to assess their quality and performance.

3.1.1 Weight Variation

Twenty intact capsules were weighed one by one, and their average weight was determined. It is crucial that no individual capsule surpasses the defined limits; the allowable percentage deviation is ±3% of the average weight. (25-28)

3.1.2 Drug content

A solid SEDDS formulation with 100 mg ALA was diluted with mobile phase, sonicated for 15 minutes for complete drug extraction, filtered through a 0.45 µm filter, and analyzed by HPLC at 215 nm for drug content.

3.1.3 Powder Flow Property Evaluation

The solid SEDDS powder was evaluated for its flow characteristics by measuring bulk density (BD), tap density (TD), Angle of Repose (AR), Hausner ratio (HR), and Carr's index (CI). These parameters provide insight into the powder's compressibility, flowability and suitability for capsule filling and processing.

3.1.4 Loss on Drying

The moisture content of the S-SEDDS was determined using thermogravimetric analysis (Mettler PM480 Delta Range, Mettler Toledo, Switzerland). One gram of the sample was evenly spread on an aluminum pan and dried at 40 °C for 2 minutes.

3.1.5 Capsule Lock Length

The S-SEDDS was filled into capsules, which were then secured. Capsule length was measured before and after filling using a screw gauge to ensure proper head-body fit and prevent overfilling.

3.1.6 Morphological Analysis

Morphological characterization was performed using a scanning electron microscope (SEM, JSM-6390). Samples were dusted onto adhesive tape on aluminium stubs, then gold-coated (>10 nm) under argon using a sputter coater at 2.0 kV and 25 mA for 10 minutes. Imaging was conducted at 20 kV accelerating voltage in the SEM chamber.

3.1.7 FT-IR Spectral Analysis

Fourier-transform infrared (FT-IR) spectroscopy analyzed the drug, polymers, excipients, and their mixtures using the KBr pellet method. Spectra were recorded from 4000 to 400 cm^{-1} with FT-IR instruments (JASCO FT/IR-4100 and Bruker). This identified characteristic functional groups, confirmed sample authenticity, and detected potential interactions by comparing peaks with reference spectra.

3.1.8 X-ray Diffraction (XRD) Analysis

XRD analysis of the optimized solid SEDDS and pure drug was performed using a D5000 Siemens diffractometer with Copper Kα radiation (1.5406 Å). Data were collected from $2\theta = 5°$ to 50° with 0.045° steps and 0.5 seconds per step. Diffractograms were compared to detect changes in peak patterns and intensities, revealing crystallinity alterations.

3.1.9 DSC Studies

DSC analysis was performed using a Q-1000 TA Instruments Perkin-Elmer Pyris DSC to assess the thermal behavior of the drug, excipients, and optimized solid SEDDS. Samples (3–5 mg) were sealed in hermetic pans with a pinhole and heated from 0°C to 210°C at 10°C/min under nitrogen flow (100 ml/min). Calibration was done with indium. The study monitored melting point, heat of fusion, loss of the drug's crystalline peak, and any new or altered peaks. The thermogram of the optimized S-SEDDS was compared to the pure drug to evaluate changes.

3.1.10 In Vitro Drug Release

An in-vitro drug release study of solid SEDDS was performed using USP dissolution apparatus type II in 900 ml of 0.1N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, and water. Capsules containing 200 mg solid SEDDS (100 mg Alpha lipoic acid) were tested at 75 rpm and 37 ± 0.5°C, with sinkers to prevent floating. Samples (10 ml) were withdrawn at 15, 30, 45, and 60 minutes, replaced with fresh medium, and analyzed by HPLC at 215 nm. The release profile was compared to pure drug.

3.1.11 Pharmacokinetic and biodistribution study

For oral administration, ALA at 100 mg/kg was suspended in 1 ml Milli-Q water and given to fasted rats. Blood (300 µl) was collected from the retro-orbital plexus at 30, 60, 120, 180, and 240 minutes, centrifuged at 10,000 rpm for 10 minutes, and plasma stored below −30°C. Plasma ALA was measured by HPLC using an internal standard method: 300 µl acetonitrile and 10 µl sodium valproate (2,500 ng/ml) were added to 90 µl plasma, centrifuged at 10,000 rpm for 5 minutes, then filtered through a 0.2 µm membrane. Quantification used a Waters HPLC system with a single quadrupole detector

and an Acquity BEH C18 column (4.6 × 250 mm, 1.7 µm).

3.1.12 Stability Studies

The optimized formulation, encapsulated in capsules, was packaged in Alu-Alu blister packaging and subjected to stability studies at conditions of 30°C±2°C/75%±2%, 25°C±2°C/60%±2%, and 40°C±2°C/75%±2% RH for a duration of 3 months.

4. Results and Discussion

4.1 Forced Degradation Study

Forced degradation studies of Alpha Lipoic Acid (ALA) revealed varying stability under different stress conditions. ALA showed moderate instability in acidic conditions (pH 1.2) with 15% degradation, suggesting partial breakdown in the stomach. It exhibited high stability in alkaline conditions with only 0.5% degradation, making it suitable for enteric release formulations. Thermal stress at 50°C for 24 hours caused significant degradation of 29.34%, indicating the need for temperature-controlled storage. Under oxidative conditions (3% H_2O_2), ALA completely degraded, confirming extreme sensitivity to oxidation and the necessity for antioxidants and oxygen-proof packaging. Hydrolytic degradation was minimal at 2.5%, showing good stability in water alone, while exposure to humidity (40°C/75% RH) led to only 0.8% degradation, demonstrating excellent stability in humid environments.

4.2 Solubility studies

Based on the findings from solubility studies, alpha lipoic acid exhibited greater solubility in MCT (oil), Cremophor RH 40 (surfactant), and PEG 400 (co-surfactant), as illustrated in Fig.1 Therefore, MCT has been chosen as the oil phase, Cremophor RH 40 as the surfactant that also functions as a permeation enhancer, and PEG 400 as the co-surfactant for subsequent studies, owing to their SEDDS that enhance drug loading efficiency. Fig.2

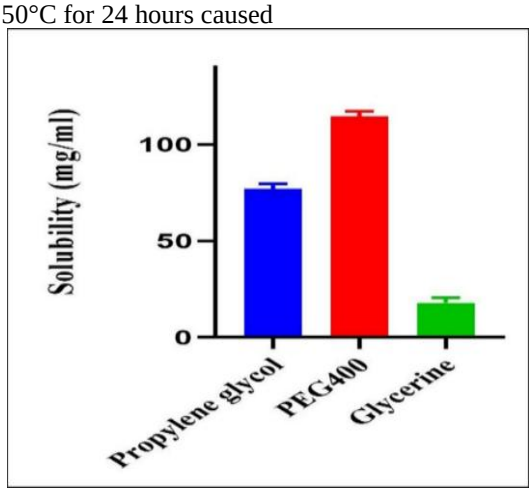

Figure 1. Solubility of Alpha Lipoic Acid (ALA) in different oils and surfactants.

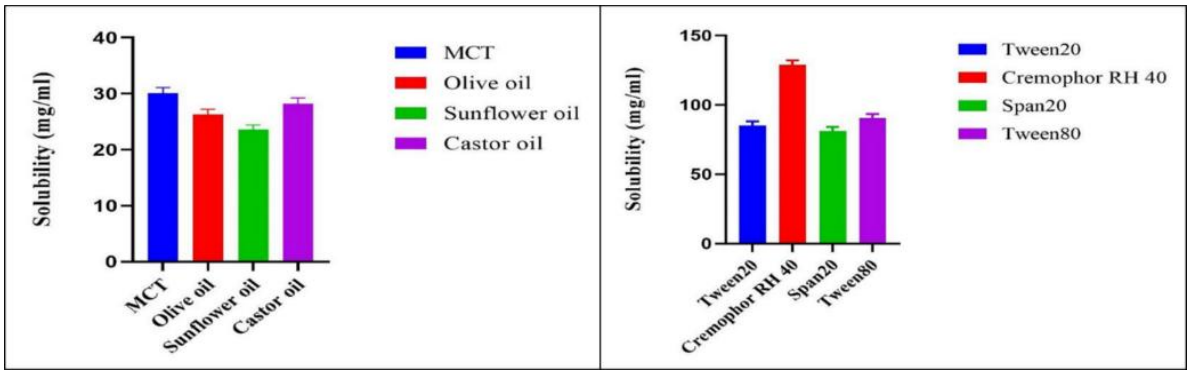

Figure 2. Solubility of Alpha Lipoic Acid (ALA) in various co-surfactants.

4.3 Preparation of solid SEDDS

S-SEDDS can be created through the solid adsorbent technique, which begins with the formulation of a liquid SEDDS that includes the drug, oil, surfactant, and co-surfactant. This liquid blend is then gradually introduced to a solid adsorbent, such as Aerosil 200 or Neusilin, while continuously mixing until a consistent, free-flowing powder is achieved. The adsorption process facilitates the transformation of the liquid SEDDS into a solid state without losing its self-emulsifying characteristics. If necessary, the mixture is dried to eliminate any remaining moisture. Ultimately, the solid SEDDS is sieved and encapsulated.

4.4 Drug-Excipient Compatibility Study (FTIR Method)

The compatibility study between the drug and excipients was conducted using Fourier Transform Infrared (FTIR) spectroscopy to evaluate any potential chemical interactions between alpha-lipoic acid (ALA) and

selected excipients, including medium chain triglyceride (MCT), PEG 400, Cremophor RH 40 and Neusilin. The FTIR spectrum of pure ALA displayed significant peaks at approximately 1695 cm^{-1}, which correspond to the C=O stretching of the carboxylic group, around 1285 cm^{-1} for C–O stretching, approximately 2950 cm^{-1} for aliphatic –CH stretching and between 925–950 cm^{-1} representing the disulfide (S–S) bond. These peaks served as reference markers to detect any potential interactions in the physical mixtures. The spectra of the excipients exhibited their respective characteristic peaks: MCT showed ester C=O stretching at around 1740 cm^{-1} and $–CH_2–$ stretching at approximately 2925 and 2850 cm^{-1}; PEG 400 presented a strong C–O–C ether stretch near 1100 cm^{-1} and a broad O–H stretch around 3400 cm^{-1}; RH 40 revealed peaks near 1730 cm^{-1} for ester groups and around 1100 cm^{-1} for ether linkages; Neusilin displayed a broad O–H band around 3450 cm^{-1} and Si–O–Si vibrations in the range of 1000–1100 cm^{-1}. The spectrum of the physical mixture (PM) maintained the primary characteristic peaks of ALA without any notable shifts, disappearances, or new peak formations, indicating that the. Bottom of Form. (Fig 3)

4.5 Evaluation of Solid SEDDS (capsule)

Estimation of Alpha lipoic acid content Assay: Pharmacopeial standards typically range from 90% to 110%. In the evaluation table, all seven batches show assay values between 97.20% and 104.87%, all of which fall within acceptable limits. Notably, Batch 5 distinguishes itself with an assay value of 100.16% ± 0.02, which is the closest to the ideal target of 100%. This suggests a high level of precision and accuracy. The assay test is essential for assessing the active pharmaceutical ingredient (API) content in each batch, ensuring that the drug dosage remains consistent and adheres to the formulation, thereby demonstrating excellent control over the manufacturing process. (Table 2)

Table 2. Assay (%) Results for Alpha Lipoic Acid Samples

Batch No.	Assay (%)
1	103.35 ± 0.02
2	104.87 ± 0.02
3	98.54 ± 0.02
4	97.20 ± 0.02
5	100.16 ± 0.02
6	98.35 ± 0.02
7	97.25 ± 0.02

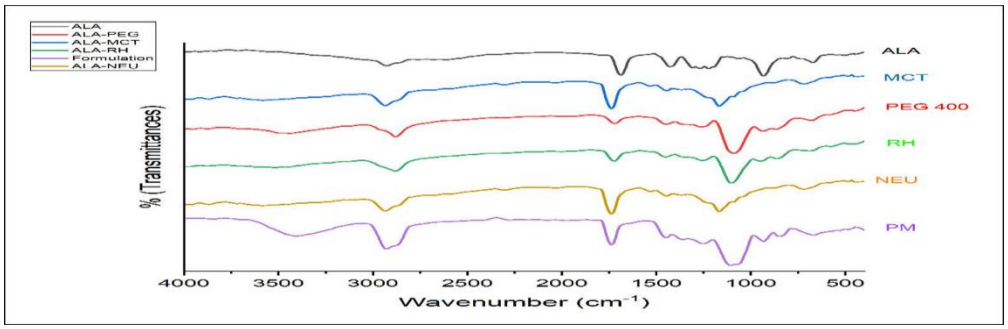

Figure 3. FTIR spectra depicting drug-excipient compatibility study of Alpha Lipoic Acid (ALA) with formulation components.

Powder Flow Properties and Density Parameters: The powder demonstrated inadequate flow characteristics, as evidenced by essential flowability metrics. The bulk density and tapped density were measured at 0.346 g/cm^3 and 0.519 g/cm^3, respectively. The Carr's Index was determined to be 19.9%, while the Hausner ratio was found to be 1.14; both of these figures indicate moderate flowability.

4.6 Loss on Drying (LOD)

The Loss on Drying (LOD) for Batch-5 was measured at 1.53% w/w, utilizing the oven drying technique at 40 °C in accordance with USP <731>. This result signifies a low moisture level in the sample, which is typically advantageous for the stability, flowability and shelf life of the powder. A low LOD value implies that the sample contains minimal volatile substances or water, thereby decreasing the likelihood of microbial growth or degradation during storage. (Table 3)

Table 3. Determination of Loss on Drying (LOD) for Powder Samples

Sr. No	LOD(%W/W)	Method
Batch 1	2.50	Oven drying at 40 °C (USP <731>)
Batch-2	2.38	
Batch-3	2.30	
Batch-4	2.21	

Batch-5	2.32	
Batch-6	2.08	
Batch-7	2.12	

4.7 Weight Variation Test

The weight variation test was conducted on seven distinct batches of capsules to verify the uniformity of fill weight, which is a crucial quality parameter for dosage precision and therapeutic consistency. In accordance with pharmacopeial standards (IP/USP), for capsules with weights ranging from 250 mg to 300 mg, the permissible limit for individual weight variation is ±7.5% of the average weight. In this investigation, all batches exhibited average weights between 268.6 mg and 280.0 mg, with standard deviations ranging from ±2.30 mg to ±4.32 mg. The calculated permissible limits for each batch confirmed that all values were well within the acceptable range. Notably, Batch 6 demonstrated the least deviation (±2.30 mg), reflecting excellent weight consistency, whereas Batch 1 displayed the highest standard deviation (±4.32 mg) yet still adhered to the limits. Consequently, all seven batches successfully passed the weight variation test, affirming the reliability and uniformity of the capsule filling process. (Table 4)

Table 4. Weight Variation Analysis of S-SEDDS Capsule Batches

Batch No.	Average Weight (mg)	Standard Deviation (± mg)	Permissible Limit (±7.5%)	Compliance
1	273.2	±4.32	252.21 – 294.39	Passed
2	275.8	±3.35	254.62 – 297.49	Passed
3	268.6	±4.20	248.45 – 288.75	Passed
4	280.0	±3.20	259.00 – 301.00	Passed
5	276.6	±3.20	255.86 – 297.59	Passed
6	271.0	±2.30	250.08 – 291.93	Passed
7	270.0	±2.34	249.75 – 290.25	Passed

4.8 Capsule Lock Length

In the evaluation of pharmaceutical capsules, maintaining consistent capsule dimensions is essential to ensure uniformity in dosage form appearance, packing and mechanical handling. For this study, seven batches of capsules were measured, each designed with a target capsule length of **19 mm**. The capsule length was assessed using a calibrated vernier caliper, and for each batch, the **average length** and **standard deviation (±SD)** were calculated. (Table 5 and 6)

Table 5. Evaluation of Powder Flow Properties Including Carr's Index and Hausner Ratio

Parameter	Carr's Index (%)	Hausner's ratio	Flowbility
Batch-1	35.29	1.54	Very poor
Batch-2	27.02	1.37	Poor
Batch-3	27	1.37	Poor
Batch-4	25.71	1.34	Poor
Batch-5	19.9	1.14	Fair
Batch-6	24.8	1.24	Passable
Batch-7	31.42	1.54	Poor

Table 6. Measurement of Capsule Length for S-SEDDS Batches

Batch No.	Average Capsule Length (mm)	Standard Deviation (± mm)	Acceptance Range (± 0.3 mm)	Compliance
1	19.02	±0.12	18.70 – 19.30	Passed
2	18.96	±0.14	18.70 – 19.30	Passed
3	19.1	±0.1	18.70 – 19.30	Passed
4	19.05	±0.09	18.70 – 19.30	Passed
5	19.00	±0.13	18.70 – 19.30	Passed
6	19.08	±0.11	18.70 – 19.30	Passed
7	19.0	±0.15	18.70 – 19.30	Passed

4.9 Blend Uniformity The evaluation of drug content uniformity was carried out for three formulation batches (Batch-F1, Batch-F2 and Batch-F3), each with a label claim of 100 mg. Samples were taken from the top, middle and bottom portions of the bulk, as well as a composite sample. The percentage of label claim observed in each portion of the three batches ranged between 97.31% and 102.65%. All individual sample values fall within the acceptable limits, indicating that the drug is uniformly distributed throughout the formulation. The composite samples also showed consistent values, with Batch-F1, Batch-F2 and Batch-F3 exhibiting 102.65%, 102.49% and 100.20% respectively. Slight variation was observed in the middle sample of Batch-F2 (101.28%), which is still within the acceptable range and does not indicate any blending or distribution issue. These results demonstrate that the formulation and manufacturing processes are highly reproducible and ensure consistent drug content across all units, thus confirming the reliability and robustness of the process. (Table 7)

Table 7. Blend Uniformity Assessment for Batches F1 to F3 (Reproducible Batches)

Sample	Batch-F1 (% of Label Claim)	Batch-F2 (% of Label Claim)	Batch-F3 (% of Label Claim)
Top	98.31	97.31	98.83
Middle	97.71	101.28	97.71
Bottom	98.13	97.34	98.13
Composite	102.65	102.49	100.20

4.10 X-ray diffraction (XRD)

X-ray diffraction (XRD) analysis was conducted on both the optimized Solid SEDDS and the pure drugs to investigate the crystalline properties of the optimized formulation. The XRD patterns show that both samples maintain the same crystalline phase, as evidenced by consistent peak positions. However, Alpha lipoic acid exhibits sharper and more intense peaks, indicating higher crystallinity. In contrast, Alpha lipoic acid SEDDs formulation the shows broader, weaker peaks, suggesting reduced crystallinity, possible lattice strain or smaller crystallite size due to self-emulsifying drug delivery. No phase transformation was observed. (Fig. 4)

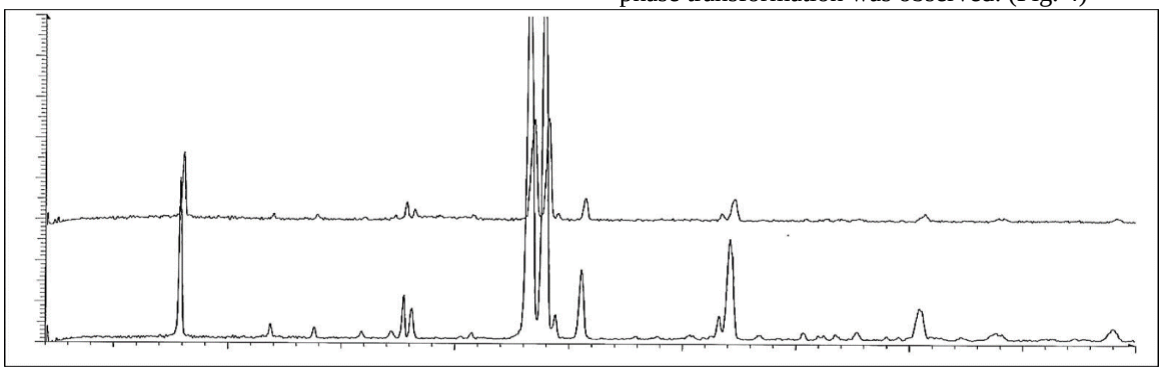

Figure 4. X-ray diffraction (XRD) patterns of pure Alpha Lipoic Acid (ALA) and its solid self-emulsifying drug delivery system (SEDDS) formulation.

4.11 DSC Studies

DSC analysis showed a sharp endothermic peak for pure ALA at 60–70 °C, indicating its melting point and crystalline nature. Neusilin UFL2 showed no peak, confirming its amorphous, inorganic nature. The physical mixture displayed a reduced/broadened peak, suggesting partial interaction. In the ALA-Solid SEDDS formulation, the ALA peak disappeared, indicating conversion to an amorphous or molecularly dispersed state, confirming successful solid dispersion and potential solubility enhancement. (Fig.5)

4.12 FT-IR Spectral Analysis: FTIR analysis was conducted to assess potential interactions between Alpha Lipoic Acid (ALA) and formulation excipients. The spectrum of pure ALA exhibited characteristic peaks at ~1700 cm^{-1} (C=O stretching), ~3000 cm^{-1} (O–H stretching) and 2920–2850 cm^{-1} (C–H stretching), along with peaks in the fingerprint region (1500–500 cm^{-1}) corresponding to C–S and S–S bonds. In the formulation, these peaks were retained with slight shifts or reduced intensity, suggesting minor physical interactions but no significant chemical changes. This indicates that ALA is compatible with the excipients and remains chemically stable in the formulation (Fig.6)

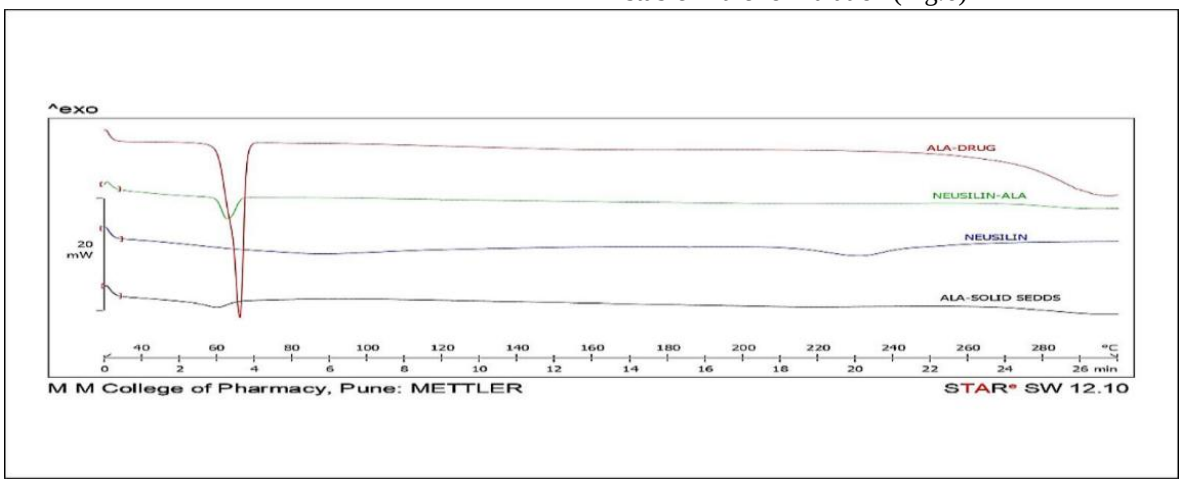

Figure 5. Differential scanning calorimetry (DSC) thermograms of solid SEDDS, pure Alpha Lipoic Acid (ALA), and Neusilin UFL2

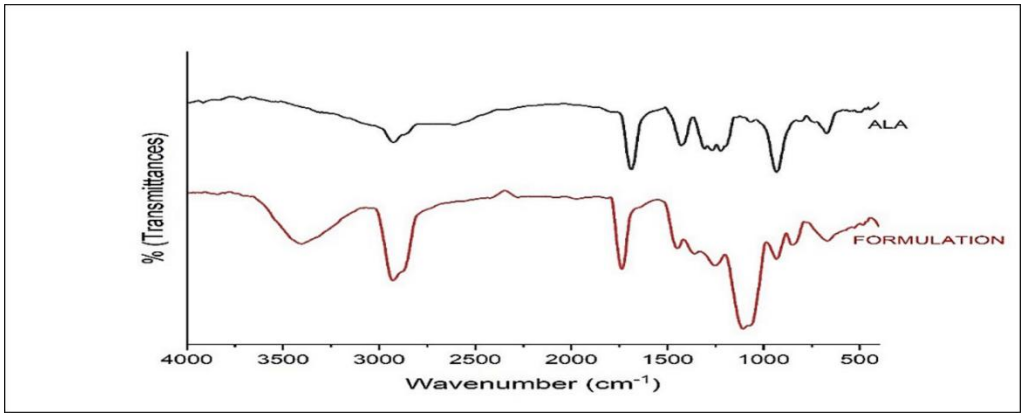

Figure 6. FTIR spectra comparison of pure Alpha Lipoic Acid (ALA) and its solid SEDDS formulation

4.13 Morphological Analysis of Solid SEDDS (S-SEDDS)

Scanning Electron Microscopy (SEM) revealed that the solid SEDDS granules possess an irregular, rough and highly porous surface with a non-spherical, aggregated structure. The particles appeared as agglomerated clusters with a flaky or flower-like morphology. This type of structure is characteristic of adsorption-based solidification using porous carriers such as Neusilin ULF2, which increases surface area and facilitates rapid emulsification upon contact with aqueous media. The absence of smooth or crystalline surfaces indicates that the drug is well-embedded or molecularly dispersed within the carrier, suggesting potential amorphization and improved solubility. (Fig.7)

4.14 In Vitro Dissolution Studies

In vitro drug release was evaluated for seven formulation batches over a 60-minute period. All batches demonstrated a rapid increase in drug release within the first 15 minutes, indicating immediate-release behavior. Among them, Batch-5 showed the highest cumulative drug release of 95.89%, followed by Batch-4 with 92.53%, while Batch-1 exhibited the lowest release at 87.15%. These findings suggest that Batch-5 possesses the most efficient dissolution profile and is potentially the most effective in enhancing drug release. (Fig.8)

The Solid-SEDDS formulation shows a significantly faster and higher drug release compared to the pure drug. Within 15 minutes, the solid SEDDS releases about 75% of the drug, whereas the pure drug releases only 32%. By 60 minutes, the solid SEDDS achieves around 90% cumulative release, while the pure drug reaches only 60%. This enhanced release from the solid SEDDS can be attributed to increased surface area, improved wettability and amorphous dispersion of the drug, which facilitates faster dissolution. In contrast, the crystalline nature and poor water solubility of the pure drug result in slower and incomplete dissolution.

The in vitro drug release study was carried out in 0.1N HCl (pH 1.2) to simulate gastric conditions. The pure drug showed only **70% drug release**, which may be attributed to its **acidic pH sensitivity and degradation in gastric fluid**. In contrast, the **Solid S-SEDDS** demonstrated a significantly higher release of **91%**, indicating improved drug protection and stability in acidic conditions. The enhanced release suggests that the S-SEDDS formulation effectively shields the drug from degradation in acidic pH, thereby improving its release and potential bioavailability in gastric conditions. (Fig. 9 and Fig. 10)

The pure drug showed only **70% drug release**, which may be attributed to its **acidic pH sensitivity and degradation in gastric fluid**. In contrast, the **Solid SEDDS** demonstrated a significantly higher release of **91%**, indicating improved drug protection and stability in acidic conditions. The enhanced release suggests that the S-SEDDS formulation effectively shields the drug from degradation in acidic pH, thereby improving its release and potential bioavailability in gastric conditions.

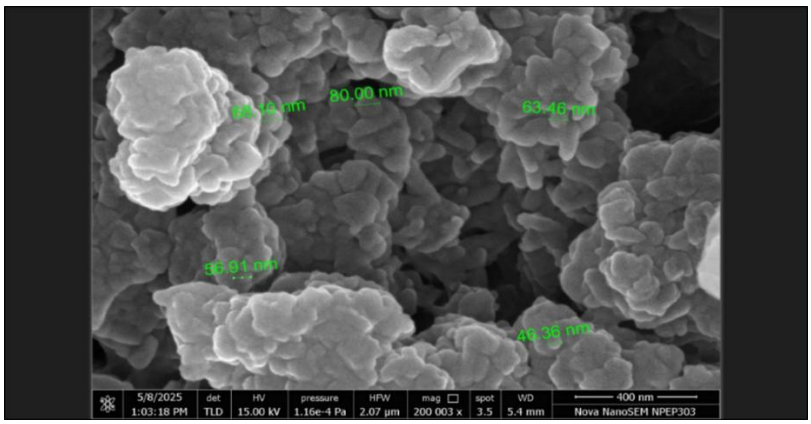

Figure 7. Scanning electron microscopy (SEM) image of solid SEDDS granules illustrating surface morphology.

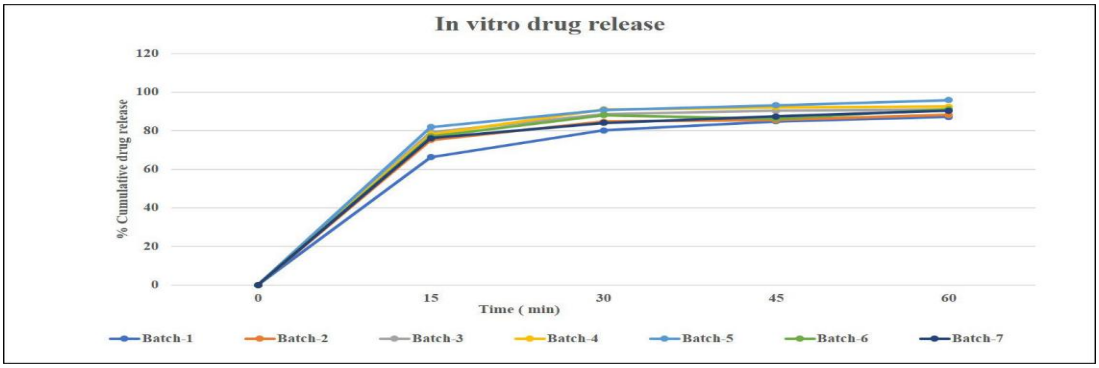

Figure 8. In vitro drug release profiles of ALA-loaded solid SEDDS batches 1 through 7

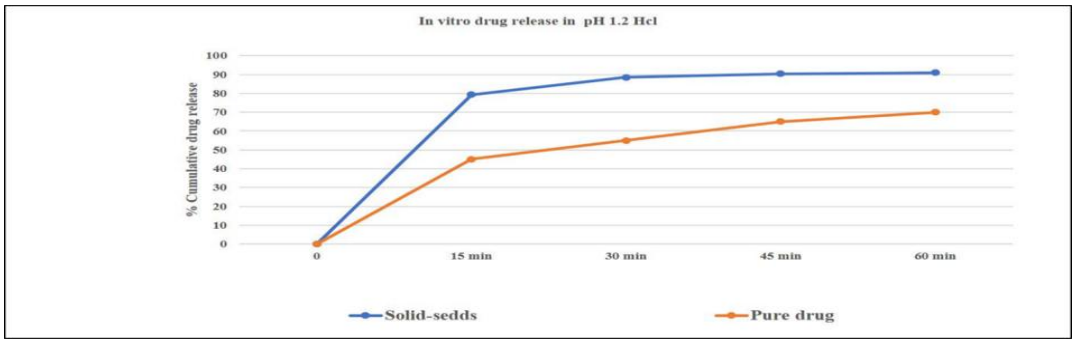

Figure 9. In vitro drug release of Alpha Lipoic Acid (ALA)-solid SEDDS in distilled water

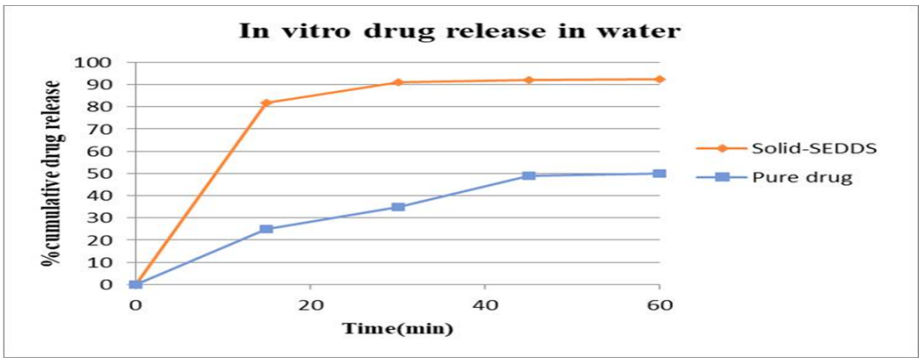

Figure 10. In vitro drug release of Alpha Lipoic Acid (ALA)-solid SEDDS in acidic medium (pH 1.2).

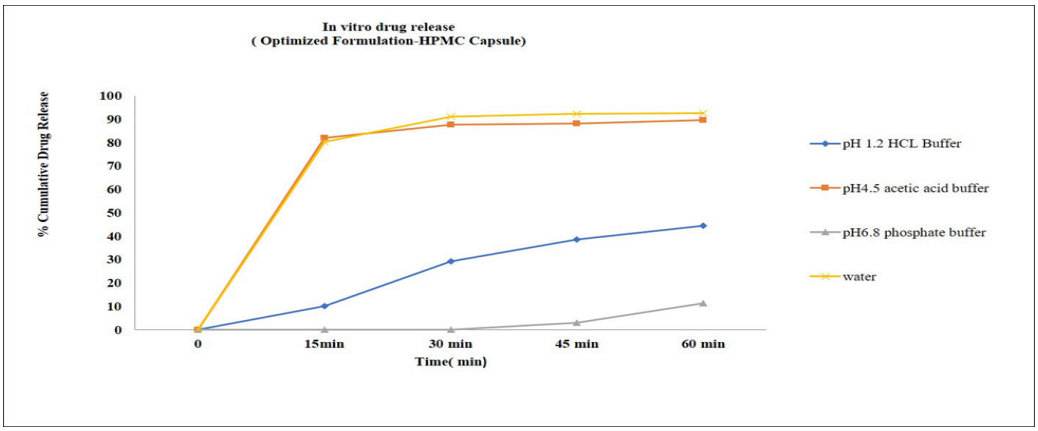

Figure 11. In vitro drug release profile of F-3 batch encapsulated in HPMC capsules across various dissolution media

The in vitro drug release profile of the optimized formulation encapsulated in HPMC capsules demonstrates pH-dependent solubility. Unlike gelatin capsules, which typically allow faster and more complete drug release across all pH conditions, the HPMC capsule shows slower drug release in acidic and alkaline media.

In pH 1.2 HCl buffer, the drug release was limited to around 45% at 60 minutes, indicating restricted release in strongly acidic environments. In pH 6.8 phosphate buffer, the release was even lower (~12%), reflecting poor solubility or delayed disintegration of the HPMC shell in alkaline conditions. In contrast, the drug showed significantly better release in water and pH 4.5 acetic acid buffer, achieving over 90% release within 60 minutes.

This suggests that the optimized HPMC formulation is more suitable for release in mildly acidic to neutral environments but not in highly acidic or alkaline media. This pH-sensitive release behavior in HPMC capsules highlights the importance of capsule type in formulation design, especially for targeted or site-specific drug delivery. (Fig.11)

4.15 Stability of ALA-S-SEDDS

Alpha Lipoic Acid Capsule (Batch F1) remained stable for 1 month under 30°C/75% RH and 40°C/75% RH. All parameters—appearance, disintegration time, dissolution and assay—were within limits. Slight decreases in dissolution and assay at 40°C were observed but still complied with specifications. (Table 8)

Table 8. Stability Study Results of S-SEDDS Capsule Formulations

Product name: Alpha Lipoic acid Capsule				
Batch number: F1			Pack type: Alu-Alu Blister	
Condition		**Initial**	**30^0C/75%**	40^0C/75%
Parameters	**Specifications**		1 Month	
Description	Hard gelatin capsule containing slightly white, free-flowing powder	Complies	Complies	**Complies**
Disintegration time	NMT 15 minutes	57 Sec	1min 08sec	**1 min 30 sec**
Dissolution	Not less than 75% (Q) of the labeled amount of alpha lipoic acid dissolved in 45 minutes	95.20	93.30	**90.21**
Assay (%) by HPLC	**90-110%**	**100.2**	**99.10**	**98.13**

5. Conclusions

The current research successfully established a Solid SEDDS for Alpha Lipoic Acid (ALA) to address its significant formulation issues, such as inadequate aqueous solubility, thermal instability and sensitivity to acid. Pure ALA exhibited limited dissolution (60%) and considerable degradation under stress conditions especially in thermal (29.34%) and acidic (17%) environments underscoring its instability and restricted oral bioavailability. The optimized S-SEDDS formulation, which includes MCT oil, Cremophor RH 40, PEG 400, and Neusilin UFL2, markedly improved the dissolution profile, achieving a drug release of 95.13%. This enhanced performance is attributed to the creation of nano-sized droplets during emulsification, which increases the surface area and transforms ALA into an amorphous state, as confirmed by Differential Scanning Calorimetry (DSC). Scanning Electron Microscopy (SEM) analysis revealed uniform, smooth particles, while assays confirmed a 100% drug content, indicating excellent content uniformity. Stability studies conducted under accelerated and ambient conditions over a month demonstrated that the formulation preserved its integrity, drug content and release performance, indicating short-term stability. In summary, the solid S-SEDDS strategy effectively improved the solubility, stability, and bioavailability of ALA, providing a promising platform for the oral delivery of other poorly water-soluble and unstable pharmaceuticals.

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Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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