Design and Development of Self Emulsifying Drug Delivery System by using QbD

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Abstract:
Approximately 40% of new chemical entities suffer from poor aqueous solubility, limiting their oral bioavailability. Self-emulsifying drug delivery systems (SEDDS), comprising oils, surfactants, and co-solvents, offer an effective strategy to enhance the absorption of hydrophobic drugs by using Qbd, while conventional SEDDS are typically in liquid form, they can pose stability and handling challenges. To address this, solid SEDDS (S-SEDDS) have been developed by solidifying liquid formulations into powders, offering improved stability and patient compliance. These systems form fine, stable oil-in-water emulsions in the gastrointestinal tract, enhancing drug solubilization and absorption.

Key Words: Drug Selection Criteria, Thermodynamic stability, pH Measurement, In vitro diffusion, Drug Content, In-vitro Dissolution, Solubility study.

INTRODUCTION

Self Emulsifying drug delivery System

Binary mixes of a lipophilic phase and a medicine are the simplest kind of SEDDS formulation, although more complicated systems including surfactants are also possible. To facilitate the formation of microemulsions, the inclusion of a co-surfactant is typically necessary. [5,6,7] These systems generally produce dispersions with lipid droplet sizes ranging from 200 nm to 5 μm, which appear turbid due to their droplet size distribution.

Oils and surfactants, in an ideal world, would produce isotropic mixes; co-solvents are another possible component of SEDDS. These substances have the remarkable ability to generate tiny oil-in-water emulsions when given to water in an environment with low turbulence, such that which is present in the digestive system.[8] Due of the decreased toxicity profile of non-ionic surfactants, medium-chain triglyceride oils and non-ionic surfactants have recently gained popularity in SEDDS.

For potential new drugs that have low water solubility, these formulations are ideal. Low and uneven bioavailability, substantial variability between and within people, and poor dosage proportionality are common challenges with oral administration of such drugs. [9,10] A number of formulation solutions have been devised to tackle these difficulties; they include cyclodextrins, nanoparticles, agents that facilitate surface tension, lipids, and permeability, micronization, salt creation, and solid dispersions.

The goal is to increase the number of medications that are not highly water-soluble, lipid-based formulations, particularly Self-Emulsifying Drug Delivery Systems (SEEDS), have been the focus of much research and development in recent years.

Isotropic blends comprising oils, both natural and manufactured, surfactants, both solid and liquid, and optionally hydrophilic co-solvents or co-surfactants make up SEEDS, which are also called self-emulsifying oil formulations. [11,12] Seeds can create microemulsions or fine oil-in-water emulsions when exposed to water and gently mixed with other substances, such gastrointestinal fluids.

Rather from causing localized gastrointestinal discomfort from prolonged contact between the undissolved medication and the gut wall, these tiny droplets can swiftly travel from the stomach into the intestines, enabling global drug distribution.

To make medications that aren't extremely water-soluble more bioavailable and soluble, forward-thinking pharmaceutical companies have developed self-emulsifying drug delivery systems (SEDDS). Isotropic oil-in-water emulsions, coupled with co-surfactants or co-solvents in some cases, can spontaneously form when these systems are gently stirred in the GI tract.

This characteristic makes SEDDS an attractive approach for addressing the challenges associated with the delivery of lipophilic drugs, which often exhibit low solubility and limited bioavailability.

Azelnidipine, a calcium channel blocker belonging to the dihydropyridine class, is widely prescribed for managing hypertension. Despite its therapeutic efficacy, its high lipophilicity poses significant challenges, particularly its poor solubility in water and limited oral bioavailability, which is approximately 50%.[13] These limitations are primarily due to extensive first-pass metabolism and insufficient dissolution in gastrointestinal fluids. To enhance its therapeutic potential, advanced drug delivery systems are essential. Among these, SEDDS has emerged as a promising strategy to improve solubility and bioavailability. By utilizing a carefully selected combination of oils, surfactants, and co-surfactants, SEDDS can form fine emulsions upon exposure to gastrointestinal fluids, facilitating rapid and efficient drug absorption. This approach addresses the inherent challenges associated with lipophilic drugs and improves their therapeutic efficacy.[14]

Medication distribution systems can benefit from a more planned and systematic approach to product performance and reliability by using QbD principles. Two foundational principles of quality by design (QbD) are determining critical quality characteristics (CQAs) and comprehending the impact of formulation elements on the final product.[15] This method makes it easier to optimize the production and formulation processes by using tools like design of experiments (DoE) and risk assessment. Applying QbD principles to the development of a SEDDS for Azelnidipine ensures the formulation effectively addresses key challenges, such as solubility and bioavailability, while also achieving consistency, regulatory compliance, and high-quality standards.

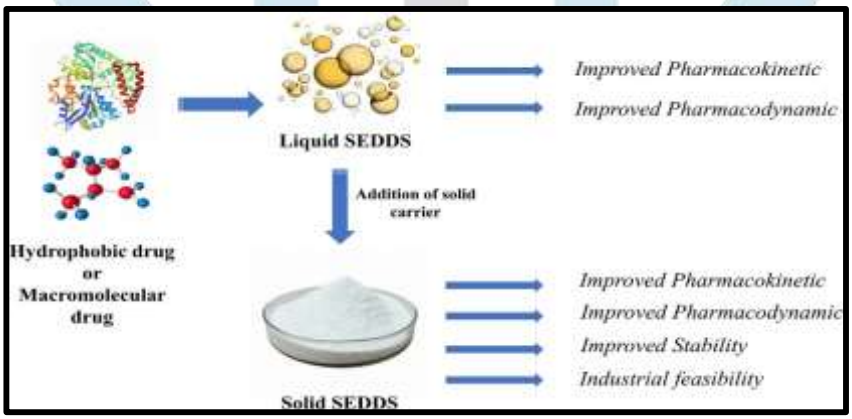

Figure 1: Self-Emulsifying drug delivery System

❖ Drug Selection Criteria for Oral SEDDS Formulation

Selecting an appropriate drug for Self-Emulsifying Drug Delivery Systems (SEDDS) involves considering various physicochemical and biopharmaceutical properties. The ideal drug candidate for SEDDS should have poor aqueous solubility but good solubility in lipids and surfactants.

1. Physicochemical Properties of Drug

A drug suitable for SEDDS should meet the following criteria:

Low Aqueous Solubility

- Poor water solubility (Biopharmaceutics Classification System BCS Class II or IV drugs).
- If a drug has high solubility in water, SEDDS may not be necessary.

High Lipophilicity (Log P > 2)

- The drug should be highly soluble in oils, surfactants, or co-surfactants to ensure good incorporation into SEDDS.

- Log P values between 2–6 is preferred.

Appropriate Molecular Weight

- **Moderate Molecular Weight (< 500 Da)**
  - Drugs with a molecular weight below 500 Dalton (Da) are generally more suitable for oral absorption.
  - These drugs can diffuse through biological membranes more efficiently, enhancing their bioavailability.
  - SEDDS can further improve their solubility and facilitate absorption, particularly for BCS Class II and IV drugs.
- **High Molecular Weight (> 500 Da)**
  - Drugs with molecular weights exceeding 500 Da often face challenges in crossing biological membranes, leading to poor permeability and limited oral bioavailability.
  - Even if solubility is improved using SEDDS, the absorption may still be restricted due to size-related permeability issues.[16,17]
  - These drugs might require additional formulation strategies such as permeability enhancers, prodrugs, or nanocarrier-based systems.

Non-Ionic Nature (Preferred)

- Strongly ionic drugs may not emulsify well in lipid systems.
- However, ionic drugs can still be incorporated if they have good solubility in SEDDS components.

Stability in Lipidic Environment

- The drug should be chemically stable in oils and surfactants over time.
- It should not degrade or precipitate upon dilution in gastric fluids.

2. Biopharmaceutical Properties of Drug

BCS Class II & IV Drugs

- **BCS Class II (low solubility, high permeability)**
  - Suitable because SEDDS enhances solubility without affecting permeability.
  - Examples: Fenofibrate, Itraconazole, Celecoxib, Nifedipine.
- **BCS Class IV (low solubility, low permeability)**
  - SEDDS can improve solubility, but permeability enhancement is also needed.
  - Permeability enhancers or lipid absorption mechanisms may be used.
  - Example: Furosemide, Paclitaxel.

Good Permeability Through the Gastrointestinal (GI) Tract

- Drugs should have moderate to high permeability to benefit from SEDDS.
- If permeability is too low, permeation enhancers (e.g., bile salts) may be needed.

No Extensive First-Pass Metabolism

- SEDDS can help drugs bypass first-pass metabolism via lymphatic absorption (if highly lipophilic).
- Suitable drugs: Cyclosporine, Tacrolimus.

Dose Requirement

- Drugs with low to moderate dose requirements (<100 mg per dose) are ideal.
- High-dose drugs may not dissolve completely in SEDDS formulation.

METHODS

Preformulation study

- **Identification of drug**

Melting Point

The melting point of Azelnidipine was determined using capillary tube method. Thieles tube containing liquid paraffin solution and then small amount of pure drug was filled in the capillary tube which is sealed at one end using flame. Sample filled in capillary is tied with thread to the thermometer and suspended into Thieles tube and heated till drug powder melts. The temperature at which the pure drug powder started melting was noted. [18,19]

λ max Wavelength determination

The sample of the standard solution were scanned between 200-400 nm regions on UV spectrophotometer (Jasco V-630). There are stock solutions of the Azelnidipine sample was prepared by dissolving 10 mg of drug in 10 ml of methanol, (1000 µg/ml respectively. Take 1ml of above solution and dilute to 10 ml methanol to make 100 µg/ml solution. Take 1ml of above dilution and dilute to 10ml methanol to make 10 µg/ml solution.[56,57]

Solubility study of the Drug

The solubility of Azelnidipine was performed in Methanol, distilled water, Phosphate buffer pH 6.8, were taken in different 50ml conical flask & 50 mg of Azelnidipine were added in it. The conical flask was stirred for 24 hrs. On mechanical shaker at 150 RPM. After 24 hrs. The flask was removed solutions were filtered and absorbance was measured at 255 nm.

- **Calibration Curve**

Calibration Curve of Azelnidipine inMethanol

Preparation of stock solution in Methanol:

Standard stock solution was prepared by taking 10 mg in 10 ml of Methanol (1000µg/ml). The stock solution scanned in the range 400-200 nm by UV spectrophotometer the solution showed maximum absorbance at 255 nm.

Preparation of dilutions for the standard curve:

From 1000µg/ml, prepare solutions of 2, 4, 6, 8, and 10 ppm by diluting 50- 300 µl stock to 10 ml Methanol. Absorbance was taken at 255 nm using Methanol as a blank. The absorbance v/s concentration graph is plotted.[20,21]

Calibration Curve of Azelnidipine in Phosphate Buffer ph 6.8

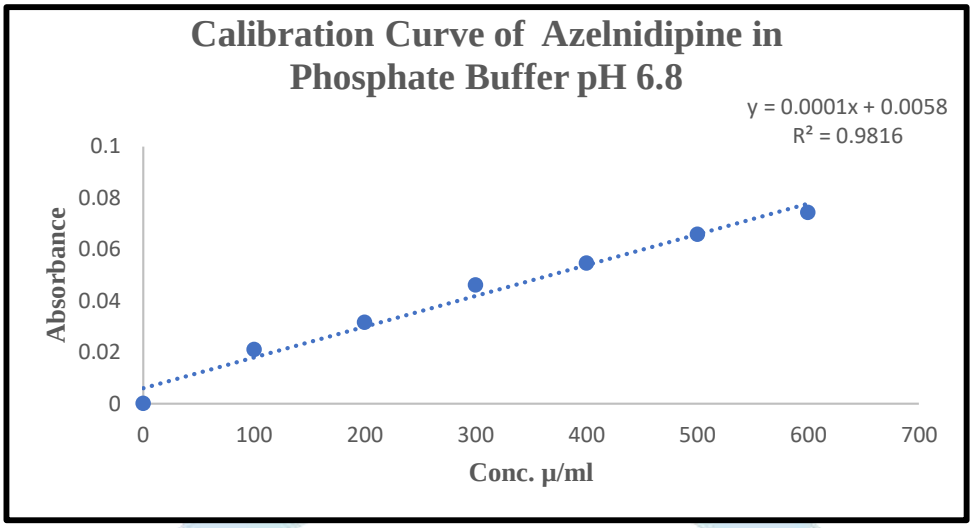

Figure 2: Calibration curve of Azelnidipine in phosphate buffer 6.8

❖ **FTIR spectroscopy**

FTIR spectroscopy was employed for the identification of Azelnidipine by comparing its characteristic absorption peaks with those of the standard reference spectrum. A small quantity (1–2 mg) of Azelnidipine was finely ground and mixed with dry potassium bromide (KBr) in a 1:100 ratio, then compressed into a thin, transparent pellet using a hydraulic press. The pellet was analyzed using an FTIR spectrophotometer over a scanning range of 4000–400 cm^{-1} at a resolution of 4 cm^{-1}. The resulting spectrum was examined for the presence of key functional group peaks corresponding to Azelnidipine, confirming the identity of the drug.

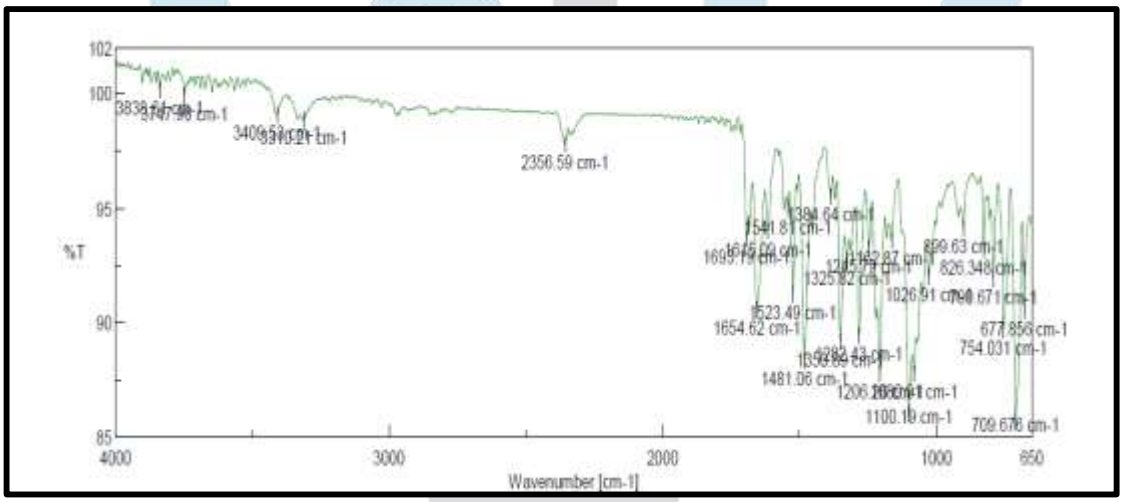

Figure 3: IR Spectroscopy of Azelnidipine

❖ **Procedure for solubility study of Azelnidipine in various excipients**

• Solubility study of drug was carried out at 37 ^{0}C for all excipients.

• Excess of drug was added separately in to 5ml of each excipient. Each sample was kept on shaking for 48 hrs at specified temperature. After 48 hrs shaking, each sample was filtered through 0.45µ Nylon Filter.

• 0.1ml of each filtered test sample was taken separately, diluted suitably with methanol and absorbance taken at respective wavelength of maximum absorption for drug.

Table 1: Different oils and their solubility mg/ml

Oil's	Solubility mg/ml
Sesame oil	3.64
Coconut oil	3.6
Olive oil	3.27
Castor oil	4.95
Sunflower oil	4.02

The solubility of the drug in different oils varied significantly, among the Oils tested, Castor oil exhibited the highest solubility (4.95 mg/mL).

Castor oil was found to be the most suitable oil phase for drug solubilization among the oils tested. These results are critical for selecting the appropriate oil phase in formulation.

Table 2: Different Surfactants and their solubility mg/ml

Surfactants	Solubility mg/ml
Tween 20	4.08
Tween 80	5.80
Span 80	5.47

The solubility of the drug in various surfactants was evaluated to identify suitable excipients for formulation development. Among the surfactants tested, Tween 80 exhibited the highest solubility (5.80 mg/mL).

Tween 80 is the most suitable surfactant among those tested for enhancing solubility and potentially improving the bioavailability of the drug in formulation.

Table 3: Different Co-Surfactants and their solubility mg/ml

Co-surfactants	Solubility mg/ml
Propylene Glycol	2.45
Iso-propyl Alcohol	6.32
PEG 400	5.18

The solubility of the drug in selected co-surfactants was evaluated to identify a suitable co-solvent for formulation development. The results are summarized in Table. Among the co-surfactants tested, isopropyl alcohol exhibited the highest solubility (6.32 mg/mL), followed by PEG 400 (5.18 mg/mL), and propylene glycol (2.45 mg/mL).

The selection of an appropriate co-surfactant is critical for enhancing the emulsification efficiency, drug loading capacity, and stability of lipid-based systems such as Self-Emulsifying Drug Delivery Systems (SEDDS). Isopropyl alcohol appears to be the most promising co-surfactant for the formulation due to its superior solubilizing capacity.

❖ DRUG EXCIPIENT COMPATIBILITY STUDY FOR CILNIDIPINE

FTIR spectroscopy

The drug excipients compatibility study was performed by FTIR technique. The optimized batch samples were scanned over wave number range of 500-4000 cm-1 with diffraction reflectance scanning technique.

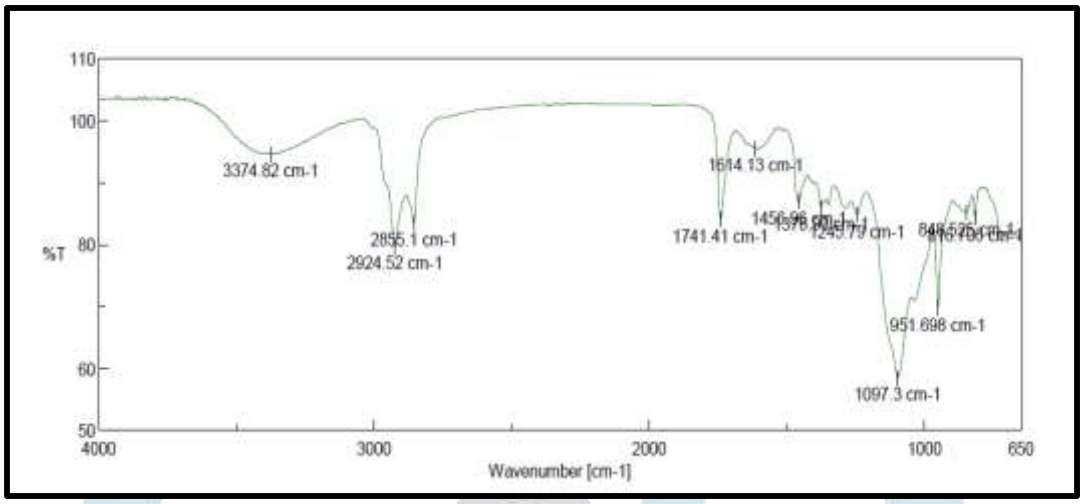

Figure 4: FTIR spectrum of a) Azelnidipine- (pure drug), b) Castor Oil c) Tween 80, d) Iso propyl Alcohol

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetric (DSC) measurements were carried out on a modulated DSC. The optimized batch sample, the aluminum pans were used and hermetically covered with lead. The heating rage was 60-300 °C for sample with constant increasing rate of temperature at 10°C/min under nitrogen atmosphere (50-60ml/min). The resultant thermograms of formulation was obtained. [22,23]

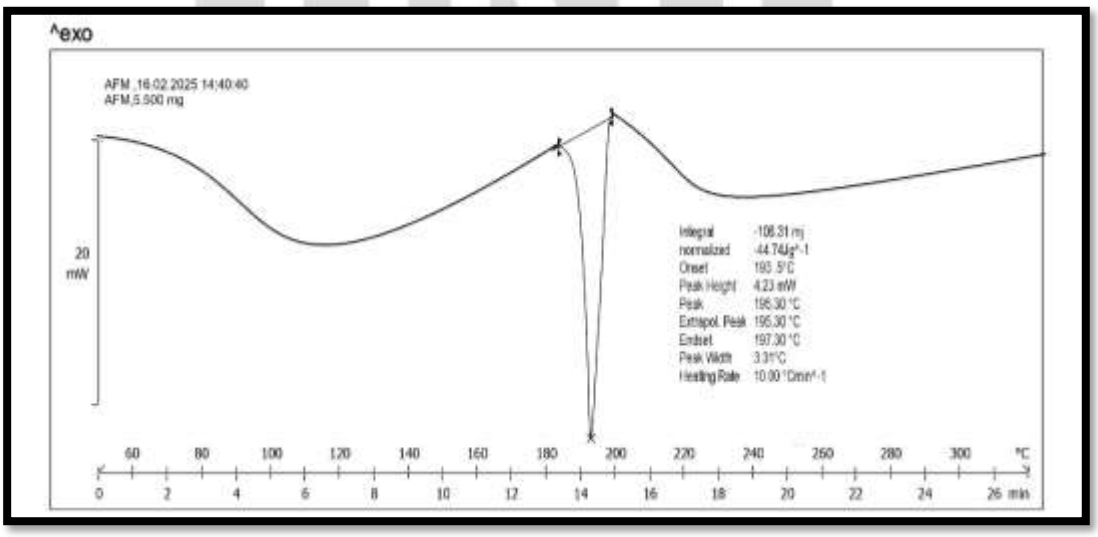

Figure 5: DSC of a) Azelnidipine- (pure drug), b) Castor Oil c) Tween 80, d) Iso propyl Alcohol

❖ Screening of Surfactant-Co-surfactant (Smix) Ratio

To determine the optimal ratio of surfactant (Tween 80) and co-surfactant (Isopropyl Alcohol) for the formulation of a self-emulsifying drug delivery system (SEDDS), a screening study was performed using castor oil as the fixed oil phase.

A fixed quantity of castor oil (200 mg) was taken in multiple screw-capped glass vials. Various Smix ratios of Tween 80 and isopropyl alcohol were prepared by mixing them in different weight ratios such

as 1:0, 1:1, 1:2 and 1:3, Each Smix combination was added gradually to the castor oil under continuous vortex mixing. The addition was carried out in small increments until a clear, transparent, and isotropic mixture was obtained, indicating the complete solubilization of the oil. [58,59]

The total amount of Smix required to solubilize the oil was recorded for each ratio. The visual appearance of the mixtures was assessed to determine clarity and phase behavior. [24,24] The Smix ratio that solubilized the oil using the least amount of surfactant-co-surfactant blend while maintaining a clear and stable system was considered optimal.

This optimized Smix ratio was then selected for further formulation development and construction of pseudo-ternary phase diagrams.

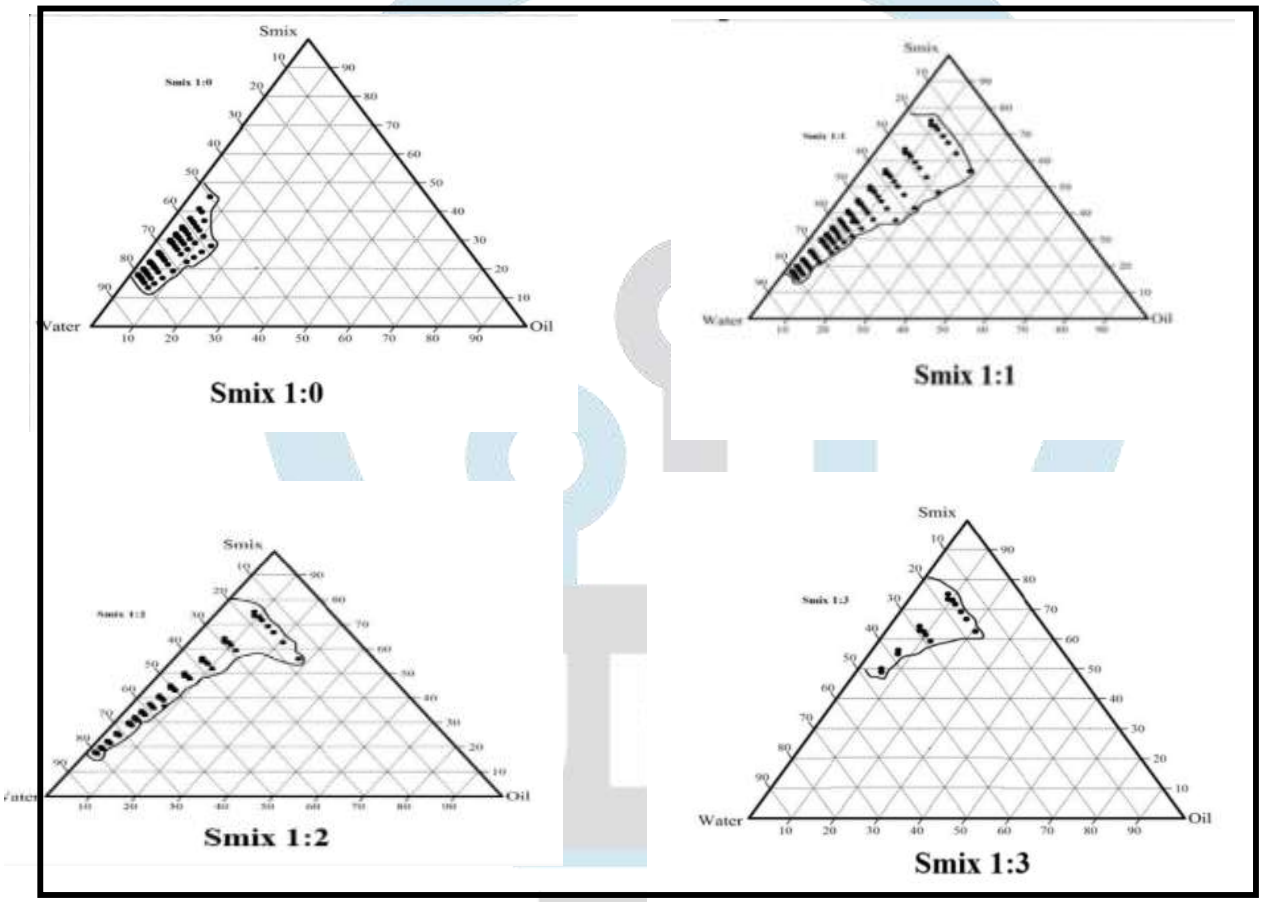

Figure 6: surfactant-cosolvent mixtures (Smix) Ratio

It was observed that the Smix of 1:1 with the selected Tween 80 and Iso propyl alcohol shows better results in terms of homogeneity as well as accommodating maximum area in phase diagram as compared to another ratio.

❖ Construction of Pseudo Ternary Phase Diagram

After identifying the optimal surfactant-co-surfactant ratio (Smix), the next step involved the screening of various oil to Smix ratios to determine the range in which a microemulsion could be formed.

A series of formulations were prepared by varying the weight ratio of castor oil to Smix from 1:9 to 9:1. In each formulation, the total weight of oil and Smix was fixed at 1 gram to ensure consistency. Based on the selected ratio (e.g., 1:9, 2:8, 3:7, …, 9:1), appropriate amounts of oil and Smix were weighed and transferred into clean screw-capped vials. [25,26,28]

To each mixture, distilled water was added dropwise under gentle stirring using a vortex mixer at room temperature. The samples were then visually observed for clarity, homogeneity, and phase behavior. The formation of a clear, transparent, and isotropic solution was considered indicative of microemulsion

formation. In contrast, samples exhibiting turbidity, phase separation, or gel formation were not considered as microemulsions.

Each formulation was tested in triplicate to ensure reproducibility. The compositions that consistently formed microemulsions were plotted on a pseudo-ternary phase diagram using castor oil, Tween 80, and isopropyl alcohol as the three components.[27] The region encompassing all successful microemulsion points was identified as the microemulsion region.

The pseudoternary phase diagrams were then constructed using these data points, and the microemulsion zone was identified and shaded on the diagram. This region indicates the optimal range of component ratios suitable for formulating a stable and effective SEDDS. Among the studied systems, the oil-to-Smix ratio of 3:7 typically showed a broad microemulsion region, highlighting it as a promising ratio for further formulation development. [59,60]

Formulation and optimization using Box–Behnken Design:

Box–Behnken Design, in this study, was utilized with Design Expert® software (Version 13.0). The Box–Behnken Design involved three independent variables: (A) Castor oil, (B) Tween 80 and (C) Iso Propyl Alcohol (IPA). The dependent variables examined were (A)Drug Content (%), (B)Self-emulsification Time (%) and (C)Drug Release (%). The Box–Behnken Design included factorial points, a center point, and axial points, resulting in a total of 13 experimental runs. The details of the independent variables, their coded levels, and the Box–Behnken Design scheme matrix are provided in the accompanying table. [28,30]

Table 4: List of Independent and Dependent variables in central composite design.

INDEPENDENT VARIABLE	LOW Level (-1)	High Level (+1)
Castor oil (ml)	0.28	0.32
Tween 80 (ml)	0.33	0.37
Iso propyl alcohol (ml)	0.33	0.37
DEPENDENT VARIABLE	Constraint	
Drug Content (%)	Maximize	
Self-emulsification time (sec)	Maximize	
Drug release (%)	Maximize	

Table 5: DOE Suggested Batches and Experimental Batches.

Formulation Code	Azelnidipine (mg)	Castor oil (ml)	Tween 80 (ml)	Iso Propyl Alcohol (ml)
F1	8	0.28	0.35	0.33
F2	8	0.32	0.33	0.35
F3	8	0.32	0.35	0.37
F4	8	0.32	0.37	0.35
F5	8	0.3	0.35	0.35
F6	8	0.3	0.33	0.37
F7	8	0.3	0.37	0.37
F8	8	0.28	0.33	0.35

F9	8	0.3	0.37	0.33
F10	8	0.32	0.35	0.33
F11	8	0.3	0.33	0.33
F12	8	0.28	0.35	0.37
F13	8	0.28	0.37	0.35

❖ Preparation of the SEDDS Formulation

First, the drug Azelnidipine (8 mg) was combined with the chosen oil phase. After that, the lipidic medication mixture was continuously vortexed on vortex mixer while the surfactant mixture was added dropwise. Selected surfactant and cosurfactant were combined in predetermined ratios to create the surfactant mixture. In the end, a transparent, uniform mixture was produced. The formulations were sealed in glass vials and stored at room temperature until used.

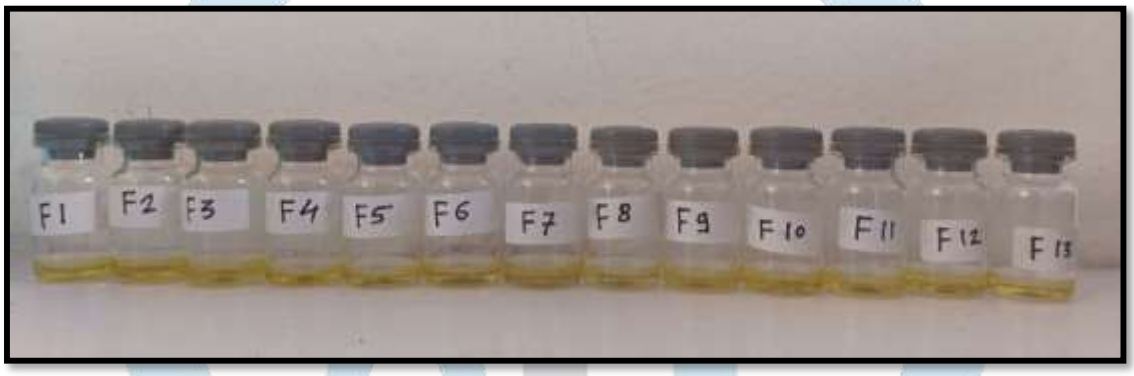

Figure 7: Formulation of Self-Emulsifying drug delivery System (SEDDS)

Method of preparation of Solid- SEDDS

Procedure:

Solidification was carried out using Aerosil 200, a hydrophilic colloidal silicon dioxide, which served as the adsorbent carrier owing to its high surface area and excellent adsorption capacity. Precisely 0.250 g of Aerosil 200 was gradually added to 1.0 mL of the Liquid-SEDDS formulation (F7) in a clean, dry mortar. The mixture was continuously triturated with a pestle under gentle pressure to allow uniform adsorption of the liquid onto the surface of the solid carrier.[60]

During mixing, the transformation of the liquid into a free-flowing powder was carefully monitored. The addition of Aerosil was done incrementally to ensure optimal adsorption and to prevent lump formation. The process continued until a uniform, dry, non-sticky, and free-flowing solid SEEDS powder was obtained. [31,32] The resultant solidified product was stored in a desiccator to avoid moisture uptake prior to further evaluations.

This method preserved the self-emulsifying ability of the liquid formulation while transforming it into a solid dosage form, facilitating improved stability, portability, and manufacturability. The optimized Solid-SEDDS of F7 was then subjected to further physicochemical evaluations, including flow properties, and in vitro release behavior, to confirm the retention of its functional properties post-solidification.[33]

Figure 8: Solid SEDDS

EVULATION OF LIQUID SEDDS

Appearance of SEEDS Formulation

The appearance of the Self-Emulsifying Drug Delivery System (SEEDS) formulation was visually inspected for clarity, colour, and phase separation. A small amount of the formulation was placed in a clean, transparent glass vial and observed under natural light. The formulation was evaluated for its homogeneity, transparency (or turbidity), and any signs of creaming, cracking, or phase separation. All SEEDS formulations appeared clear, homogeneous, and physically stable with no signs of turbidity, phase separation, or particulate matter. This indicates efficient emulsification and good physical stability of the formulations. [34,35]

Clarity of SEEDS Formulation

The clarity of the SEEDS formulation was assessed visually to determine the degree of transparency after dilution. A fixed amount of the formulation (e.g., 1 mL) was diluted in 100 mL of distilled water under gentle stirring at room temperature. The resulting emulsion was immediately observed against a black and white background under adequate lighting. The clarity was graded based on visual inspection as clear, slightly turbid, or turbid. All formulations appeared clear with no turbidity, indicating efficient self-emulsification and uniform dispersion.

Thermodynamic stability studies

To evaluate the stability of the formulations, three standard tests were conducted[36.37,38]

Heating-Cooling Stability: The stability of the SEEDS formulations was evaluated by subjecting each sample to six heating-cooling cycles between 4°C and 45°C, with a 48-hour holding period at each temperature. The formulations were observed after each cycle for signs of phase separation, creaming, or sedimentation. All formulations remained physically stable throughout the cycles, indicating good thermal stability.[56]

Centrifugation Stability: SEEDS formulations were subjected to centrifugation at 3500 rpm for 30 minutes at room temperature to assess physical stability under accelerated conditions. The samples were examined for any signs of layering or sedimentation. All formulations remained stable, showing no phase separation or physical instability.

Freeze-thaw Stability: SEEDS formulations were subjected to three freeze-thaw cycles, alternating between -21°C and +25°C, each held for 48 hours. After each cycle, samples were inspected for crystallization, phase separation, or texture changes. All formulations remained stable, indicating good resistance to temperature stress. [39]

Droplet Size, Zeta Potential, and Polydispersity Index (PDI)

The droplet size, polydispersity index (PDI), and zeta potential of the SEEDS formulation were determined using a dynamic light scattering (DLS) technique with a Zetasizer (e.g., Malvern Zetasizer Nano ZS or equivalent).[40] An appropriate quantity of the formulation was diluted 100 times with distilled water to ensure suitable scattering intensity and avoid multiple scattering effects. The diluted sample was transferred to a clean disposable cuvette for droplet size and PDI measurement, and to a folded capillary cell for zeta potential analysis.

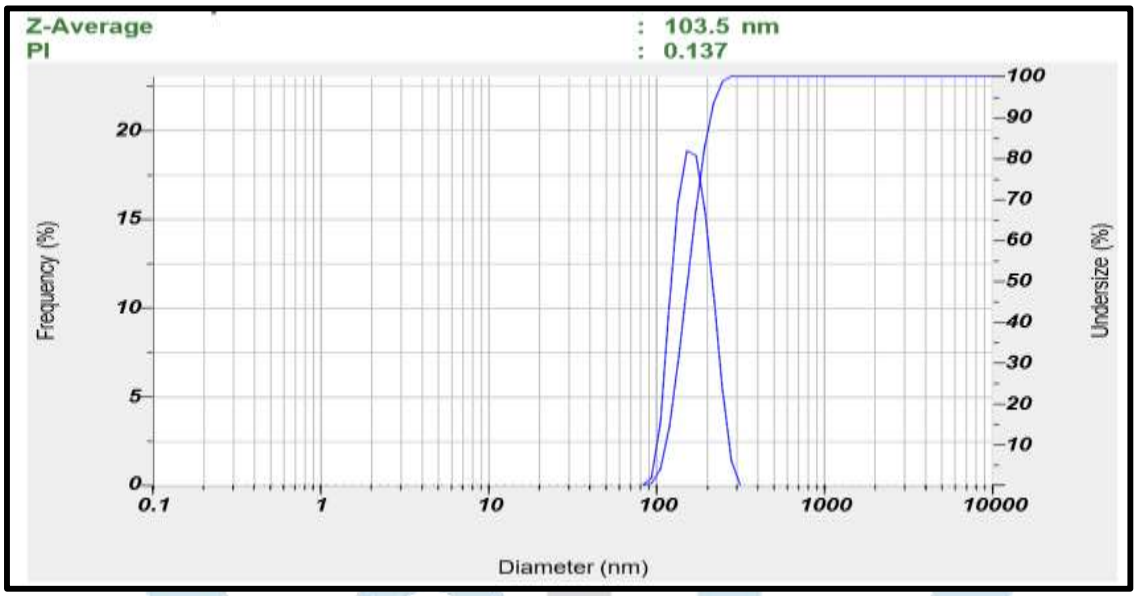

Figure 9: Particle Size PDI of optimized batch F7

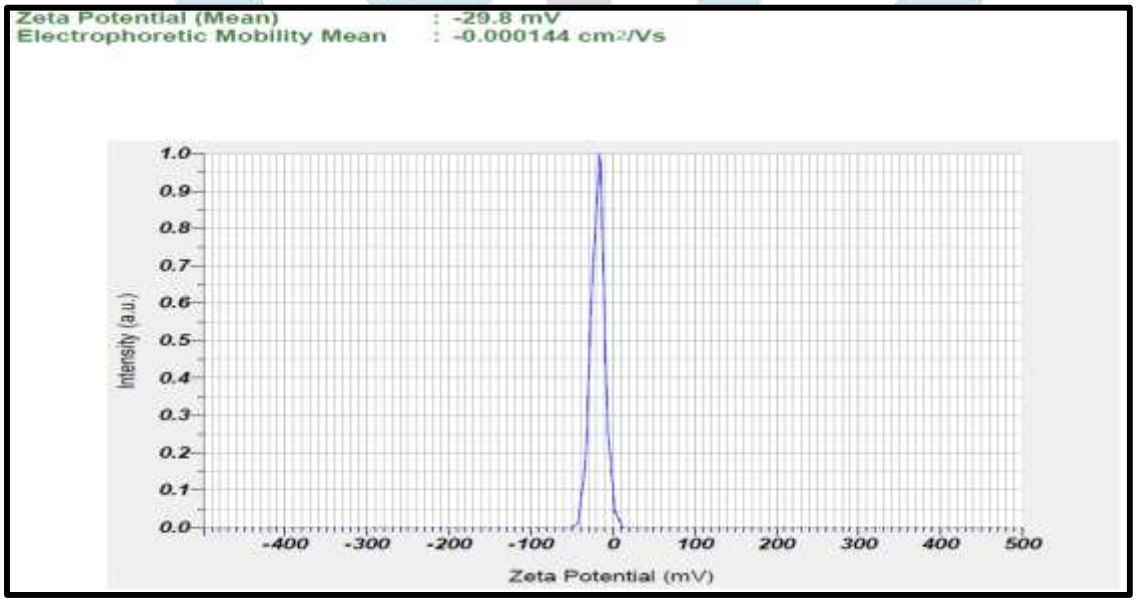

Figure 10: Zeta potential of optimized batch F7.

The droplet size ranged from 103.5 nm to 195.4 nm, with PDI values indicating a relatively narrow size distribution (0.12 to 0.497). The zeta potential values ranged from -29.8 mV to -16.4 mV, suggesting moderate to good electrostatic stability. Among these, batch F7 showed the smallest droplet size (103.5 nm), low PDI (0.137), and a high negative zeta potential (-29.8 mV), indicating it as the optimized formulation with superior stability and homogeneity.

Conductivity Measurement

The electrical conductivity of the SEEDS formulation was measured to determine the nature of the emulsion formed upon dilution (i.e., oil-in-water or water-in-oil). A fixed volume of the formulation (e.g., 1 mL) was diluted with 100 mL of distilled water under gentle stirring to simulate in vivo dispersion. The conductivity

of the resulting emulsion was measured using a digital conductivity meter (e.g., Contech Digital Conductivity Meter) at room temperature (25 ± 1 °C).

High conductivity values typically indicate the formation of an oil-in-water (o/w) emulsion, while low conductivity values suggest a water-in-oil (w/o) system. The measurements were performed in triplicate, and the mean conductivity value was recorded in microsiemens per centimeter (µS/cm).

The conductivity values ranged from 40.0 ± 0.8 to 99.0 ± 0.6 µS/cm, indicating that most formulations formed oil-in-water emulsions. Batch F7 showed the highest conductivity (99.0 ± 0.6 µS/cm), supporting its efficient self-emulsification and o/w emulsion formation.

pH Measurement

The pH of the SEEDS formulation was measured to assess its suitability for oral administration and to ensure stability. A specific quantity of the formulation (e.g., 1 mL) was diluted with 100 mL of distilled water to simulate dispersion conditions. The pH of the resulting emulsion was determined using a calibrated digital pH meter (e.g., Contech Digital PH Meter) at room temperature (25 ± 1 °C).

The pH meter was calibrated with standard buffer solutions before use. Measurements were conducted in triplicate, and the average pH value was recorded. [40,41]

The pH values of the formulations ranged from 6.88 ± 0.52 to 7.16 ± 0.26, indicating a near-neutral pH suitable for oral administration and formulation stability.

Viscosity Measurement

The viscosity of the SEEDS formulation was measured to assess its flow behavior and suitability for encapsulation or filling. Viscosity was determined using a Brookfield viscometer (e.g., Brookfield DV-E) equipped with a suitable spindle. The measurement was carried out at room temperature (25 ± 1 °C) at a fixed rotation speed (e.g., 50 rpm).

A sufficient volume of the undiluted formulation was placed in the sample container, and viscosity was recorded in centipoise (cP). All measurements were performed in triplicate, and the mean value was reported. [42,43,44]

The viscosity values ranged from 41.0 ± 1.1 to 71.0 ± 1.6 cP, indicating moderate flow properties suitable for formulation handling and processing.

In vitro diffusion study (Drug Release)

- **i.** Using a vertical Franz diffusion cell, the drug release from the SEDDS formulation was assessed in a Phosphate buffer solution (PBS) with a pH of 6.8.
- **ii.** A recently made phosphate buffer with a pH of 6.8 was utilized as the receptor media.
- **iii.** It was on the Franz's Diffusion cell assembly that the dialysis membrane. (Molecular weight 12000, pore size 2.4nm) was soaked in the receptor media overnight.
- **iv.** The system was maintained on the multistation diffusion study apparatus at 37^0C ± 2^0C with stirring at 100 rpm after 2 milliliters of the SEDDS formulation was added to the donor compartment.
- **v.** Two milliliter portions of the medium were removed at specific intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours) and promptly replaced with an identical volume of fresh medium.
- **vi.** After the portions were appropriately diluted with the solution, they were examined using a UV-Vis Spectrophotometer set at 255nm (λmax). The mechanism of drug release from the SEDDS

was determined by fitting the data acquired from the in-vitro diffusion investigations to various kinetic equations.[45,46]

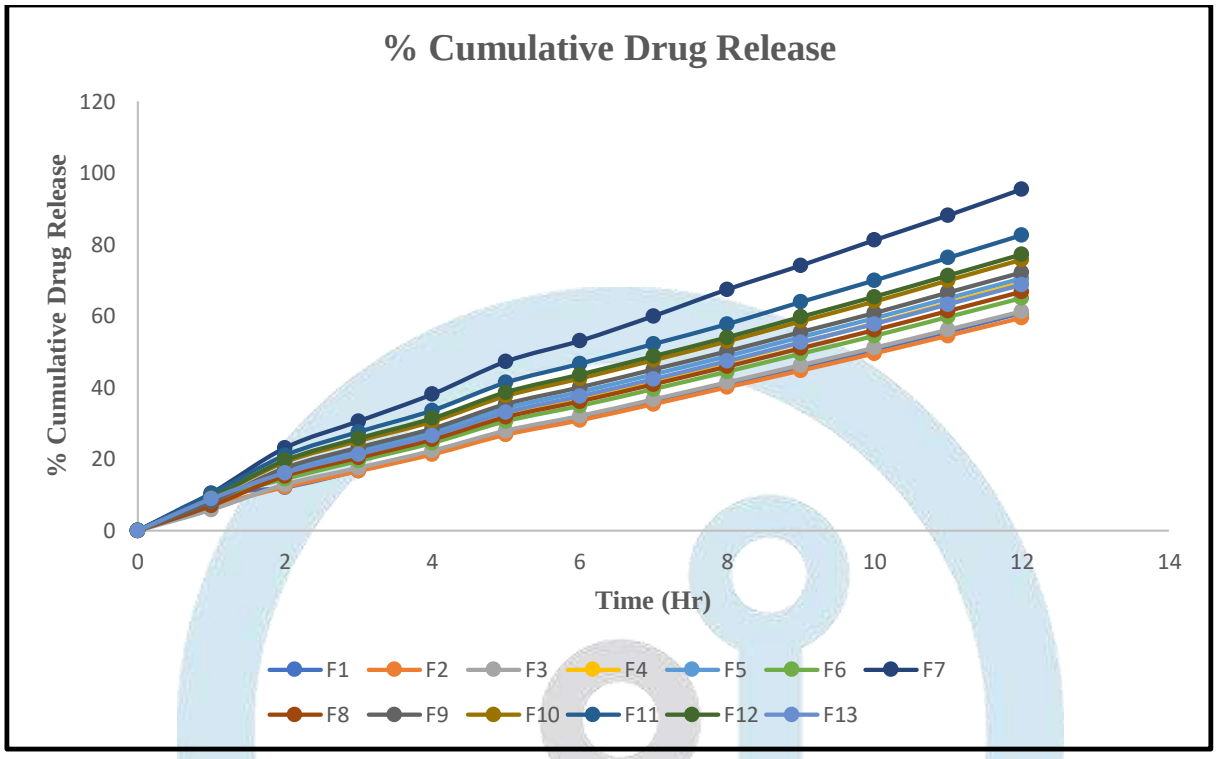

Figure 11: *in-vitro* release profile of formulations F1-F13

The in-vitro drug release of thirteen formulations (F1–F13) was evaluated over 12 hours. Formulation F7 showed the highest cumulative drug release at 95.51%, indicating superior release performance. Formulations F11 (82.67%), F12 (77.24%), and F10 (75.83%) also demonstrated good release profiles, while F1, F2, and F3 showed slower release rates (around 59-61%). The enhanced release in F7 is attributed to its optimal droplet size and surfactant concentration, promoting better drug solubilization and diffusion. These results suggest F7 as the most promising sustained-release SEDDS formulation.

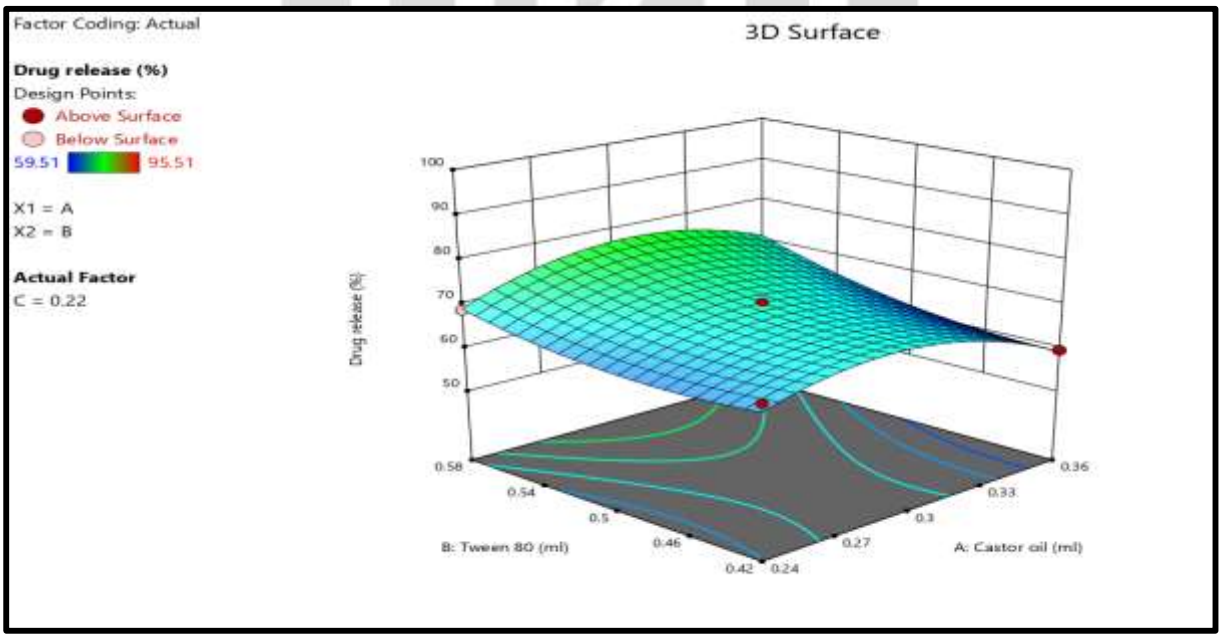

Figure 12: 3D Surface plot of Drug release

Drug Content

I. Self-emulsifying drug delivery systems formulation 100 µL was taken and dissolved in 10 ml of methanol.

II. Samples were prepared in triplicate and absorbance measured at 255 nm using UV-

visible spectrophotometer (Jasco V-630).

III. Methanol was used as a reference solution.

The drug content of SEDDS formulations (F1–F13) varied significantly, ranging from 35.54% (F6) to 89.71% (F7), reflecting the impact of excipient type and ratio on drug solubilization and entrapment. Formulation F7 showed the highest drug content, indicating optimal Azelnidipine solubilization and compatibility with excipients. F13 also had a high drug content (79.48%), while F6, F5, and F3 exhibited lower values (35.54–45.54%) likely due to poor solubilization. These results emphasize the critical role of excipient selection, with F7 identified as the most efficient formulation for drug incorporation.

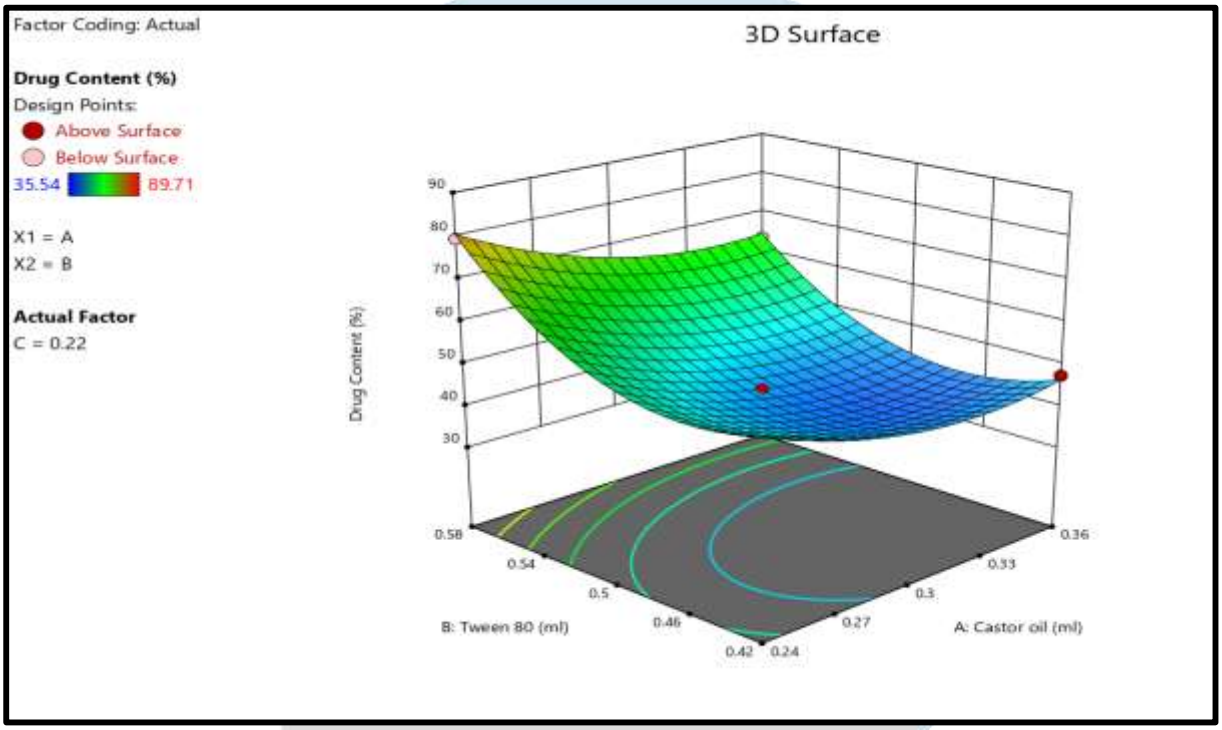

Figure 13: 3D Surface plot of Drug Content

Self-Emulsification Time

The self-emulsification time of the SEEDS formulation was determined by adding 1 mL of the formulation dropwise into 250 mL of distilled water maintained at 37 ± 0.5 °C with gentle stirring (50 rpm) using a magnetic stirrer. The time taken for the formulation to form a clear or slightly turbid emulsion, indicating complete self-emulsification, was recorded using a stopwatch. [47,48] The process was visually observed against a white background. The test was performed in triplicate, and the average self-emulsification time was reported.

The self-emulsification time of SEDDS formulations (F1–F13) ranged from 29.0 ± 0.8 seconds (F7) to 71.0 ± 1.0 seconds (F11). Formulation F7 showed the fastest emulsification, followed by F4 and F9, indicating efficient and rapid emulsion formation that can enhance drug solubilization and bioavailability. In contrast, F11, F8, and F6 had slower emulsification times, likely due to higher viscosity or less optimal surfactant-to-oil ratios, which may hinder drug release. Overall, most formulations emulsified within one minute, with F7 emerging as the most promising for rapid dispersion and improved absorption of Azelnidipine.

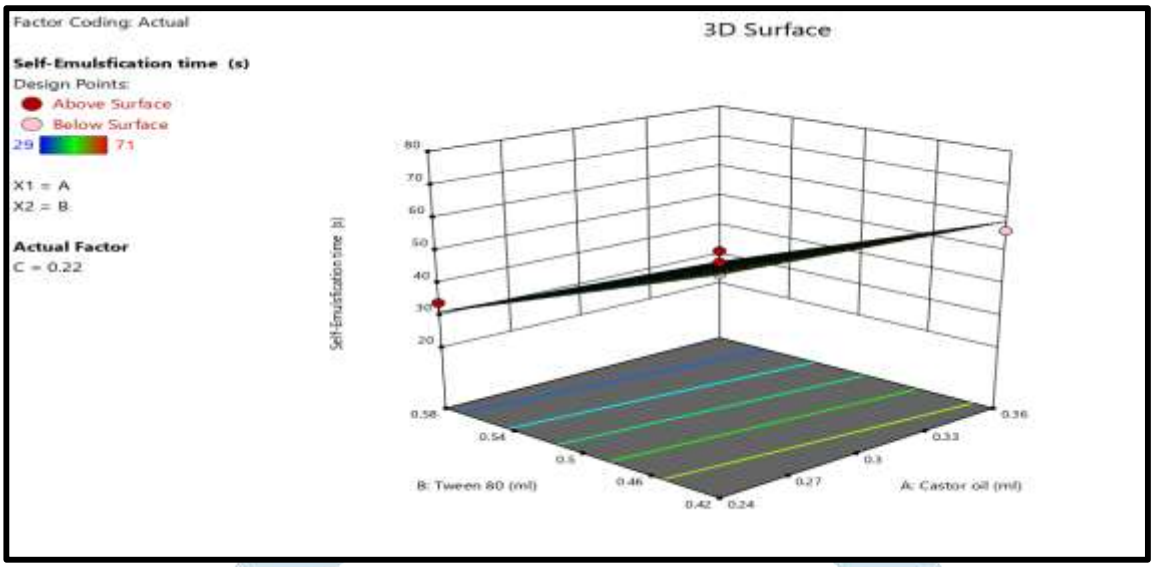

Figure 14: 3D Surface plot of Self-Emulsification time

❖ EVULATION OF SOLID-SEDDS

In-vitro Dissolution Study

A dissolution test was performed using dissolution test apparatus USP type II in Phosphate buffer pH 6.8 and 8mg Azelnidipine marketed tablet and optimized SEDDS Capsule formulation. Dissolution studies were conducted using USP apparatus type-II; at 37±0.5°C temperature at 50 rpm.[50,51]

Media. The 5 ml solution was withdrawn at time intervals of 10, 20, 30, 40, 50, and 60 min. The dissolved amount of the drug was quantitated by using UV visible spectroscopy at 255 nm.

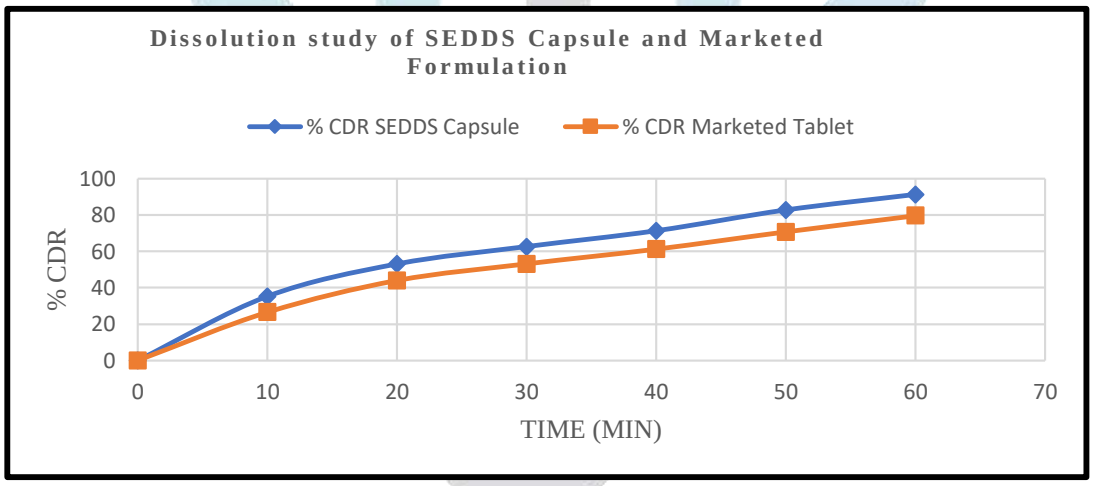

Figure 15: Comparative Dissolution Study of Formulated SEDDS Capsule with Marketed Tablet

The in vitro dissolution of the optimized SEDDS capsule (F7) was compared with a marketed Azelnidipine tablet over 60 minutes. The SEDDS showed a faster and higher drug release, with 35.16% released at 10 minutes versus 26.46% for the tablet, and reaching 91.11% at 60 minutes compared to 79.54% from the marketed product. This improved dissolution is due to the self-emulsifying nature of F7, which forms a fine emulsion that enhances surface area, wettability, and solubilization of Azelnidipine. Additionally, the reduced droplet size and high surface charge of F7 contributed to its rapid and efficient drug release.

CONCLUSION

This study successfully developed and optimized a Self-Emulsifying Drug Delivery System (SEDDS) for Azelnidipine to improve its oral bioavailability. Using a Quality by Design approach with Box-Behnken Design, formulation F7 was identified as optimal, showing a droplet size of 103.5 nm, low PDI (0.137), and high zeta potential (-29.8 mV), indicating excellent stability. FTIR and DSC analysis confirmed drug-excipient compatibility. The optimized SEDDS showed rapid emulsification, high clarity, and superior drug release (91.11% at 60 min) compared to the marketed tablet (79.54%). Solidification with Aerosil 200 preserved its properties and improved handling. Overall, SEDDS proved to be an effective strategy for enhancing Azelnidipine's solubility and bioavailability.

REFERENCES

1. Asghar AA et al. (2022). Formulation of ciprofloxacin-loaded oral self-emulsifying drug delivery system to improve the pharmacokinetics and antibacterial activity. Frontiers in Pharmacology, 13:967106.
2. Balakrishnan P et al. (2009). Enhanced oral bioavailability of dexibuprofen by a novel solid self-emulsifying drug delivery system (SEDDS). Eur J Pharm Biopharm, 72(3):539-45.
3. Bashir MA et al. (2023). Development and evaluation of self-emulsifying drug-delivery system–based tablets for simvastatin, a BCS Class II Drug. Drug Design, Development and Therapy, Dec 31:261-72.
4. Chilamula S. (Master's thesis). Formulation development of simvastatin self-emulsifying drug delivery system using Hot melt extrusion. University of Mississippi.
5. Cholakova D et al. (2022). Self-emulsification in chemical and pharmaceutical technologies. Current Opinion in Colloid & Interface Science, 59:101576.
6. Diril M et al. (2023). Development, Characterization and In-vitro Evaluation of Solid Self-Emulsifying Drug Delivery Systems (S-SEDDS) Containing Valsartan. Erzincan Univ J Sci Tech, 16(3):672-86.
7. Essien ES et al. (2024). Development and evaluation of encapsulated self-emulsifying drug delivery system of hydrochlorothiazide. Nigerian J Pharm Res, 20(1):23-30.
8. Gade MM, Hurkadale PJ (2016). Formulation and evaluation of self-emulsifying orlistat tablet to enhance drug release and in vivo performance: factorial design approach. Drug Deliv Transl Res, 6(3):276–288.
9. Gao H et al. (2021). Integrated in silico formulation design of self-emulsifying drug delivery systems. Acta Pharm Sin B, 11(11):3585-94.
10. Gursoy RN, Benita S (2004). Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed Pharmacother, 58(3):173-82.
11. Iqbal S et al. (2023). A comprehensive review of the self-emulsifying drug delivery system (SEDDS) and its recently developed formulations. IJPIHS, 5(1):45-58.
12. Kallakunta VR et al. (2023). Formulation and processing of solid self-emulsifying drug delivery systems (HME S-SEDDS). Int J Pharm, 641:123055.
13. Kohli K et al. (2010). Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability. Drug Discov Today, 15(21–22):958–65.
14. Kumar A, Sharma S, Kamble R (2010). Self emulsifying drug delivery system (SEDDS): future aspects. Int J Pharm Pharm Sci, 2(4):7–13.
15. Malkawi A et al. (2022). Development of Self-Emulsifying Drug Delivery Systems (SEDDSs) Displaying Enhanced Permeation of the Intestinal Mucus. Molecules, 27(14):4611.
16. Mathew RO, Varkey JO (2022). Formulation and in vitro evaluation of self nano emulsifying drug delivery system of quercetin. Int J Curr Pharm Sci, 14(1):60-9.

17. Morgen M et al. (2017). Lipophilic salts of poorly soluble compounds to enable high-dose lipidic SEDDS formulations in drug discovery. Eur J Pharm Biopharm, 117:212-23.
18. Nigade PM et al. (2012). Self emulsifying drug delivery system (SEDDS): A review. Int J Pharm Biol Sci, 2(2):42-52.
19. Park H, Ha ES, Kim MS (2020). Current status of supersaturable self-emulsifying drug delivery systems. Pharmaceutics, 12(4):365.
20. Patel PA et al. (2008). Self emulsifying drug delivery system: A review. Res J Pharm Technol, 1(4):313-23.
21. Rahman MA et al. (2013). Role of excipients in successful development of self-emulsifying/microemulsifying drug delivery system (SEDDS/SMEDDS). Drug Dev Ind Pharm, 39(1):1–19.
22. Reddy MR, Gubbiyappa KS (2021). A comprehensive review on supersaturable self-nanoemulsifying drug delivery system. BCS, 4:5.
23. Rehman FU et al. (2022). Self-emulsifying drug delivery systems (SEDDS): measuring energy dynamics. Pharmaceuticals, 15(9):1064.
24. Ratna Sree V, Sunitha Reddy M (2022). Formulation and Evaluation of SMEDDS of Ticagrelor. Saudi J Med Pharm Sci, 8(11):628–43.
25. Sharma M, Singh B (2022). Formulation and Evaluation of SEDDS for Candesartan Cilexetil. Nanotechnology, 15(2):2244.
26. Sharma PK, Kar M, Jain DK (2014). SEDDS: a review. J Appl Pharm Res, 2(4):01–9.
27. Singh B et al. (2009). SEDDS: formulation development, characterization, and applications. Crit Rev Ther Drug Carrier Syst, 26(5).
28. Singh B et al. (2014). Recent advances in SEDDS. Crit Rev Ther Drug Carrier Syst, 31(2).
29. Singh MK et al. (2021). Formulation and Evaluation of SEDDS of Commiphora Wightti Extract. J Adv Sci Res, 12(01):140–9.
30. Sinka D et al. (2022). Formulation, characterization and permeability studies of fenugreek-containing SEDDS. Molecules, 27(9):2846.
31. Tang B et al. (2008). Development of solid SEDDS: preparation techniques and dosage forms. Drug Discov Today, 13(13–14):606–12.
32. Uttreja P et al. (2025). SEDDS: Transition from Liquid to Solid – A Comprehensive Review. Pharmaceutics, 17(1):63.
33. Yang X et al. (2021). Preparation and evaluation of SEDDS of cepharanthine. AAPS PharmSciTech, 22:1–2.
34. Uttreja P et al. (2025). Self-Emulsifying Drug Delivery Systems (SEDDS): Transition from Liquid to Solid—A Comprehensive Review of Formulation, Characterization, Applications, and Future Trends. Pharmaceutics, 17(1):63.
35. Yang X et al. (2021). Preparation and evaluation of self-emulsifying drug delivery system (SEDDS) of cepharanthine. AAPS PharmSciTech, 22:1–2.
36. Hawley AE, Davis SS, Illum L. Targeting of colloids to lymph nodes: influence of lymphatic physiology and colloidal characteristics. Adv Drug Deliv Rev. 1995;17(1):129–48.
37. Thi TD, Van Speybroeck M, Barillaro V, Martens J, Annaert P, Augustijns P, Van Humbeeck J, Vermant J, Van den Mooter G. Formulateability of ten compounds with different physicochemical profiles in SMEDDS. Eur J Pharm Sci. 2009;38(5):479–88.
38. Dintaman JM, Silverman JA. Inhibition of P-glycoprotein by D-alphatocopheryl polyethylene glycol 1000 succinate (TPGS). Pharm Res. 1999;16(10):1550–6.
39. Chervinsky DS, Brecher ML, Baker RM, Hoelcle MJ, Tebbi CK. Reversal of C1300 murine neuroblastoma multidrug resistance by cremophorEL, a solvent for cyclosporin A. Cancer Biother. 1993;8(1):67–75.
40. Ghosh PK, Majithiya RJ, Umrethia ML, Murthy RS. Design and development of microemulsion drug delivery system of acyclovir for improvement of oral bioavailability. AAPS PharmSciTech. 2006;7(3):77.

41. Jing Q, Shen Y, Ren F, Chen J, Jiang Z, Peng B, Leng Y, Dong J. HPLC determination of anethole trithione and its application to pharmacokinetics in rabbits. J Pharm Biomed Anal. 2006;42(5):613–7.
42. Mercke Odeberg J, Lignell A, Pettersson A, Hoglund P. Oral bioavailability of the antioxidant astaxanthin in humans is enhanced by incorporation of lipid based formulations. Eur J Pharm Sci. 2003;19(4):299–304.
43. Shen HR, Li ZD, Zhong MK. Preparation and evaluation of selfmicroemulsifying drug delivery systems containing atorvastatin. Yao Xue Xue Bao. 2005;40(11):982–7.
44. Singh AK, Chaurasiya A, Jain GK, Awasthi A, Asati D, Mishra G, Khar RK, Mukherjee R. High performance liquid chromatography method for the pharmacokinetic study of bicalutamide SMEDDS and suspension formulations after oral administration to rats. Talanta. 2009;78(4–5):1310–4.
45. Wei L, Li J, Guo L, Nie S, Pan W, Sun P, Liu H. Investigations of a novel self-emulsifying osmotic pump tablet containing carvedilol. Drug Dev Ind Pharm. 2007;33(9):990–8.
46. Kuehl PJ, Brenner T, Jain PK, Karlage K, Sepassi K, Yang G, Mayersohn M, Yalkowsky SH, Myrdal PB. Formulation and in vivo evaluation of chlorpropham (CIPC) oral formulations. J Pharm Sci. 2008;97(12):5222–8.
47. Porter CJH, Charman SA, Williams RD, Bakalova MV, Charman WN. Evaluation of emulsifiable glasses for the oral administration of cyclosporin in beagle dogs. Int J Pharm. 1996;141(1–2):227–37.
48. Porter CJ, Kaukonen AM, Boyd BJ, Edwards GA, Charman WN. Susceptibility to lipase-mediated digestion reduces the oral bioavailability of danazol after administration as a medium-chain lipid-based microemulsion formulation. Pharm Res. 2004;21(8):1405–12.
49. Cuine JF, McEvoy CL, Charman WN, Pouton CW, Edwards GA, Benameur H, Porter CJ. Evaluation of the impact of surfactant digestion on the bioavailability of danazol after oral administration of lipidic selfemulsifying formulations to dogs. J Pharm Sci. 2008;97(2):995–1012.
50. Araya H, Tomita M, Hayashi M. The novel formulation design of selfemulsifying drug delivery systems (SEDDS) type O/W microemulsion II: stable gastrointestinal absorption of a poorly water soluble new compound, ER-1258 in bile-fistula rats. Drug Metab Pharmacokinet. 2005;20(4):257–67.
51. Araya H, Nagao S, Tomita M, Hayashi M. The novel formulation design of self-emulsifying drug delivery systems (SEDDS) type O/W microemulsion I: enhancing effects on oral bioavailability of poorly water soluble compounds in rats and beagle dogs. Drug Metab Pharmacokinet. 2005;20(4):244–56.
52. Singh AK, Chaurasiya A, Awasthi A, Mishra G, Asati D, Khar RK, Mukherjee R. Oral bioavailability enhancement of exemestane from self-microemulsifying drug delivery system (SMEDDS). AAPS PharmSciTech. 2009;10(3):906–16.
53. Ratanabanangkoon P, Guzman H, Almarsson O, Berkovitz D, Tokarcyzk S, Straughn AB, Chen H. A high-throughput approach towards a novel formulation of fenofibrate in omega-3 oil. Eur J Pharm Sci. 2008;33(4–5):351–60.
54. Khoo S-M, Humberstone AJ, Porter CJH, Edwards GA, Charman WN. Formulation design and bioavailability assessment of lipidic selfemulsifying formulations of halofantrine. Int J Pharm. 1998;167(1–2): 155–64.
55. Ma EL, Ma H, Liu Z, Zheng GX, Duan MX. In vitro and in vivo evaluation of a novel oral insulin formulation. Acta Pharmacol Sin. 2006;27(10):1382–8.
56. Park MJ, Ren S, Lee BJ. In vitro and in vivo comparative study of itraconazole bioavailability when formulated in highly soluble selfemulsifying system and in solid dispersion. Biopharm Drug Dispos. 2007;28(4):199–207.
57. Woo JS, Song Y-K, Hong J-Y, Lim S-J, Kim C-K. Reduced food-effect and enhanced bioavailability of a self-microemulsifying formulation of itraconazole in healthy volunteers. Eur J Pharm Sci. 2008;33(2):159–65.
58. Heo MY, Piao ZZ, Kim TW, Cao QR, Kim A, Lee BJ. Effect of solubilizing and microemulsifying excipients in polyethylene glycol 6000 solid Self-Emulsifying Drug Delivery Systems 519 dispersion on enhanced dissolution and bioavailability of ketoconazole. Arch Pharm Res. 2005;28(5):604–11.

59. Patil PR, Praveen S, Shobha Rani RH, Paradkar AR. Bioavailability assessment of ketoprofen incorporated in gelled self-emulsifying formulation: a technical note. AAPS PharmSciTech. 2005;6(1): E9–13.
60. Matuszewska B, Hettrick L, Bondi JV, Storey DE. Comparative bioavailability of L-683,453, a 5alpha-reductase inhibitor, from a self-emulsifying drug delivery system in beagle dogs. Int J Pharm. 1996;136(1–2):147–54.