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Development and Optimization of Solid Self-Nanoemulsifying Drug Delivery System (Solid-SNEDDS) for Enhancing Oral Bioavailability of Poorly Water-Soluble Itraconazole

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ABSTRACT

This study aimed to develop and optimize a Solid-Self Nanoemulsifying Drug Delivery System (Solid-SNEDDS) to enhance the solubility, dissolution rate, and bioavailability of itraconazole. The optimized formulation (SF1) was prepared using Capmul MCM, Tween 20, and Propylene Glycol as excipients. Solubility studies indicated the highest solubility in Capmul MCM (8.7 mg/ml). SF1 demonstrated a drug content of 95.15% ± 0.12 and an entrapment efficiency of 89.56% ± 0.12, suggesting efficient drug loading and minimal leakage. In vitro dissolution studies showed a maximum drug release of 98.82% at 8 hours, surpassing the marketed formulation's 98.5%. Particle size analysis revealed a mean size of 95.2 nm with a PDI of 0.115, indicating uniform distribution, while a zeta potential of -29.3 mV suggested good colloidal stability. FTIR and DSC analyses confirmed the stability and compatibility of formulation components. Stability studies over three months indicated no significant changes in drug content, entrapment efficiency, or drug release. The results suggest that the optimized Solid-SNEDDS formulation significantly improves the solubility and bioavailability of itraconazole, offering a promising strategy for the oral delivery of lipophilic drugs.

Keywords: *Itraconazole, Solid-SNEDDS, Solubility Enhancement, Bioavailability, Drug Delivery System, Particle Size, Entrapment Efficiency, In Vitro Dissolution, Stability Studies.*

1. INTRODUCTION

Poor water solubility and low oral bioavailability of Biopharmaceutics Classification System (BCS) Class II drugs, such as itraconazole, pose significant challenges in drug formulation and therapeutic efficacy. Itraconazole, a potent antifungal agent, exhibits high permeability but limited aqueous solubility, resulting in insufficient drug dissolution in the gastrointestinal tract and reduced systemic absorption. Enhancing the solubility and bioavailability of such drugs is crucial for achieving optimal therapeutic outcomes. [1-5]

Lipid-based drug delivery systems, particularly Self-Nanoemulsifying Drug Delivery Systems (SNEDDS), have gained attention for their ability to improve the solubility, dissolution rate, and oral bioavailability of lipophilic drugs. SNEDDS are isotropic mixtures of oils, surfactants, and co-surfactants that spontaneously form fine oil-in-water nanoemulsions upon mild agitation in gastrointestinal fluids. The nano-sized droplets generated by SNEDDS provide a large surface area for drug release and absorption, effectively bypassing the dissolution step that limits the bioavailability of poorly water-soluble drugs.[6-8]

Despite the advantages of liquid SNEDDS, they pose challenges such as stability issues, leakage, and difficulties in handling and transportation. To address these limitations, **Solid-SNEDDS** have been developed by converting liquid SNEDDS into solid forms through techniques like adsorption onto solid carriers, spray drying, freeze-drying, and extrusion. Solid-SNEDDS offer improved stability, ease of handling, better patient compliance, and the potential for various solid dosage forms such as capsules, tablets, and powders.[9-10]

The transformation of liquid SNEDDS to Solid-SNEDDS involves the use of porous carriers that can adsorb the lipid-based mixture without affecting its self-emulsifying properties. The selection of suitable oils, surfactants, and co-surfactants is

crucial and is typically guided by solubility studies of itraconazole in different lipid excipients. **Pseudo-ternary phase diagrams** are constructed to identify the optimal concentrations of these excipients, ensuring the formation of a stable nanoemulsion with desirable characteristics. [11-14].**The objective of this research** is to develop and optimize a Solid-SNEDDS formulation for itraconazole to enhance its oral bioavailability. Key evaluation parameters include droplet size analysis, zeta potential measurement, drug content determination, in-vitro dissolution studies, and thermodynamic stability tests. The optimized formulation is expected to exhibit improved dissolution profiles and bioavailability compared to conventional itraconazole formulations.[15]

In conclusion, the development of Solid-SNEDDS for itraconazole represents a promising strategy to overcome solubility and bioavailability challenges, providing an effective and stable oral delivery system for lipophilic drugs.

2. MATRIALS AND METHODS

2.1 MATRIALS

The Itraconazole drug sample was supplied by Solanki Enterprise in Pune. Capmul CMC, Tween 80, Propylene Glycol, Capryol 90, Maisine 35-1, Lutrol E-400, and Labrafac, Acetone, Methanol, Ethanol, Aerosil 200 and Potassium Dihydrogen Phosphate were sourced from Cosmo Chem. Pvt. Ltd.

2.2 METHODS [16]

Step-1: Determination of Itraconazole solubility in different oils

Excess amount of Itraconazole was added to 1ml of oils. The suspension was equilibrated on a mechanical shaker for 24 h at 25 ^{0}C and resulting suspensions were filtered through 0.5 µm Whatmann filter paper no.41. The filtrate (0.1 ml) was diluted with 10 ml of distilled water to determine the dissolved amount of Itraconazole using UV visible spectrophotometer (Jasco V- 630) at 265 nm.

Step-2: Identification of micro-emulsion region

Solubility study, oil, surfactant and cosurfactant were selected to construct a pseudo ternary phase diagram. Capmul MCM were selected as oil phase; Tween 20 and Propylene Glycol were selected as surfactant and co-surfactants respectively. From pseudo-ternary phase diagram, a stable micro- emulsion zone was identified. For the identification of a micro emulsion zone, surfactant to co- surfactant ratio (S mix) was kept at 1:1. The S mix concentration was increased from 1 to 9 by keeping oil phase as constant. Oil and surfactant mixture were mixed at a ratio of 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8 and 1:9, Respectively. Furthermore, study was carried out by keeping S mix as constant 1:1. Oil and surfactant mixture was mixed at a ratio of 1:1, 2.5:1, and 3.5:1 [9]. To each of the mixture distilled water was added drop wise until the first sign of turbidity occurred; the solution was allowed to equilibrate and if turbidity changed to a clear solution again, excess amount of water was added to the observed turbidity.

Step-3: Preparation of liquid L-SNEDDS and S-SNEDDS

Based on the phase diagram, oil and Smix ratio were selected as vehicle at which wide micro emulsion region is observed were selected as the vehicle for the formulation of L-SNEDDS. Itraconazole was added to the oil phase and sonicated for 10 min. To it, surfactant and co-surfactant were added in the proportions shown in Table 1. The resultant mixtures were heated over a water bath maintained at 40°C for 10 min to facilitate solubilization of ITZ, and vortexed for 15 min until ITZ was completely dissolved.

2.3 Method of preparation of S- SNEDDS [17]

Conversion of Liquid-SNEDDS to Solid-SNEDDS

Solidification of selected L-SNEDDS (Batch IF6) was done by the solid carrier adsorption method. Briefly, 7 g of L-SNEDDS formulation was blended with 2g of microcrystalline cellulose to obtain a wet mixture. Later, 5 g of Aerosil 200 was added to the wet mixture and mixed to obtain S- SNEDDS.

Table 1: Formulation of table of S-SNDDS.

Formulation code	Optimized L-SNDDS (gm)	microcrystalline cellulose (gm)	Aerosil 200 (gm)
SF1	7	2	5

2.4 EVULATION OF SOLID-SNEDDS

2.4.1 Drug content [18]

The weighed amount of 10 mg formulations powder was taken in a volumetric flask of 10 ml and the volume was made up by methanol and sonicator for 15 min., after that 1 ml of this mixture was diluted to 10 ml by methanol, and the percentage drug content was observed at 265 nm using UV spectrophotometer (Jasco V-630). Calculate drug content by the calibration curve.

2.4.2 Entrapment Efficiency (%EE) [19]

The entrapment efficiency of optimized S-SNDDS formulation was determined by centrifugation method, in which 10 mg in 10 ml of the prepared optimized S-SNDDS formulation was placed in the Eppendorf for centrifugation (RM-12) at 1400 rpm for 30min after centrifugation, the supernatant liquid was separated, containing the un-entrapped drug, diluted with Methanol and analyzed using UV spectrophotometer at 265 nm. By using that absorbance entrapment efficiency (%EE) are calculated by using the following formula.

$$EE(\%)\frac{Total\ drug\ added - amount\ of\ free\ drug}{Total\ drug\ added}\times 100 \quad \ldots (1)$$

2.4.3 In-vitro Dissolution Study [20]

A dissolution test was performed using dissolution test apparatus USP type II in Phosphate buffer pH 6.8 and ITZ (100 mg) and optimized S-SNDDS formulation (SF1). Dissolution studies were conducted using USP apparatus type-II; at 37±0.5°C temperature at 50 rpm. 100mg plain drug was added to the dissolution apparatus containing 900 ml of dissolution Media. The 5 ml solution was withdrawn at time intervals of 1,2,3,4, 5, 6, 6 and 8 hrs. The dissolved amount of the drug was quantitated by using UV visible spectroscopy at 265 nm.

2.4.4 Particle size and zeta potential (Malvern zeta sizer) [21]

The weighed amount of 10 mg optimized S-SNDDS formulation (SF1) was taken and mixed with distilled water and sonication was kept for 30 min. The analysis was performed at a temperature of 25°Csame procedure repeated at zeta potential. The prepared formulations were characterized for zeta-potential in order to know the stability of the formulations.

2.4.5 Field Emission Scanning Electron Microscopy (FESEM) [22]

Field emission scanning electron microscopy is used to determine the morphology of fractured, surface topography, and texture. The surface morphology of optimized S-SNDDS formulation (SF1) was determined by a FESEM (Carl Zeiss, supra55, Germany) at the central instrumental facility (Savitribai Phule Pune University). Photographs of samples were taken by a different magnification power (10 000x).

2.4.6 FTIR spectroscopy [23]

The drug excipients compatibility study was performed by FTIR technique. The SF1 samples were scanned over wave number range of 500-4000 cm-1 with diffraction reflectance scanning technique.

2.4.7 Differential Scanning Calorimetry (DSC) [24]

Differential scanning calorimetric (DSC) measurements were carried out on a modulated DSC (Mettler Toledo, SW STARe, and USA). The SF1 were weighed (2-8mg), the aluminum pans were Used and hermetically covered with lead. The heating rage was 50-250 °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.

2.4.8 XRD [25]

SF1 were compared in the crystallographic investigation using an X-ray diffractometry (XRD) (Bruker D8 Advance) with Cu-K radiation (λ=1.54) at a voltage of 40 kV, 50 mA, at increments of 0.02º from 5º to 100º diffraction angle (2θ) at 1 s/step. SF1 were scanned against a zero backdrop.

2.4.9 Stability studies [26]

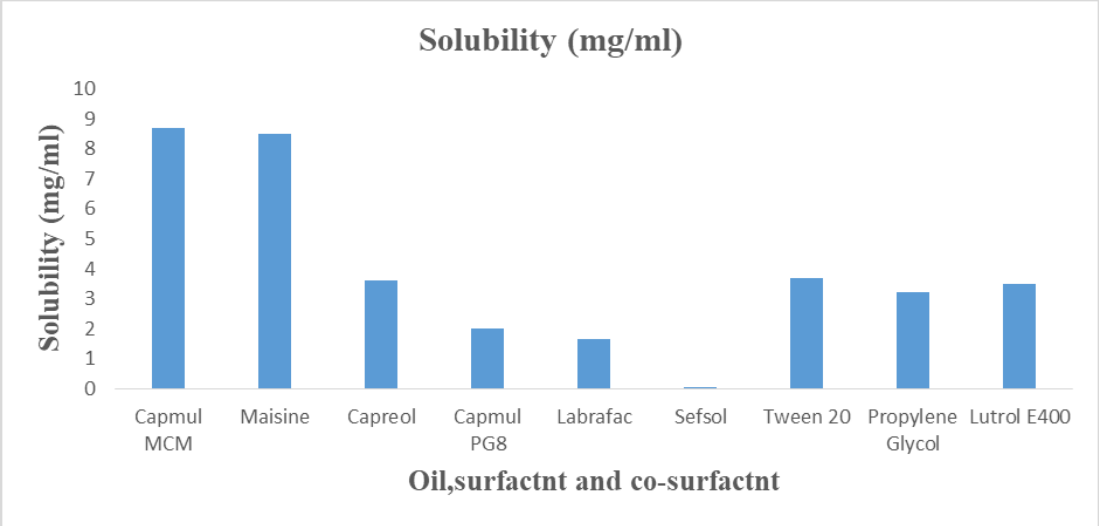
The optimized S-SNDDS formulation (SF1) were stored at room temperature (25°C) and refrigerator temperature (2–8°C) for 1 month and Drug content, Entrapment efficiency (EE%) and Drug Release(%) were determined. The optimized S-SNDDS formulation (SF1) were stored at room temperature for 30 days, and Drug content, Entrapment efficiency (EE %) and Drug Release (%) is calculated

3. RESULT AND DISCUSSIONS

3.1 Solubility of ITZ in different, oils, Surfactant and co-surfactant

Table 2: Solubility of ITZ in various oils, surfactant and co-surfactant.

Name Of Oil,surfactnt and co-surfactant	Solubility (mg/ml)
Capmul MCM	8.7
Maisine	8.5
Capreol	3.6
Capmul PG8	2
Labrafac	1.65
Sefsol	0.07
Tween 20	3.7
Propylene Glycol	3.2
Lutrol E400	3.5



3.2 Evulation of S-SNDDES

3.2.1 Drug Content

Table 3: Drug content of SF1.

Formulation Code	SF1
SF1	95.15±0.12

Conclusions

The drug content of formulation SF1 was found to be 95.15% ± 0.12, indicating efficient drug loading and uniform distribution within the formulation. This high drug content suggests good formulation stability and minimal drug loss during the preparation process.

3.2.2 Entrapment efficiency

Table 4: Entrapment efficiency of SF1.

Formulation Code	SF1
SF1	89.56±0.12

Conclusion

The entrapment efficiency of SF1 was found to be 89.56%, indicating effective drug encapsulation within the formulation. This high entrapment efficiency suggests minimal drug loss during formulation and ensures a sustained and controlled release profile. A high entrapment efficiency is crucial for maintaining therapeutic efficacy, reducing dosing frequency, and improving bioavailability. Overall, SF1 demonstrates a well-optimized formulation with efficient drug loading, making it a promising candidate for further development.

3.2.3 In vitro Dissolution Study

Table 5: Drug release of SF1 and Marketed formulation.

Time (hrs)	SF1	Marketed formulation
0	0	0
1	16.39±0.12	15.23±0.42
2	32.14±0.36	31.87±0.09
3	40.92±0.03	39.66±0.03
4	49.21±0.69	48.52±0.12
5	58.82±0.02	56.78±0.02
6	69.72±0.09	65.71±0.13
7	86.44±0.36	82.12±0.78
8	98.82±0.12	98.5±0.69

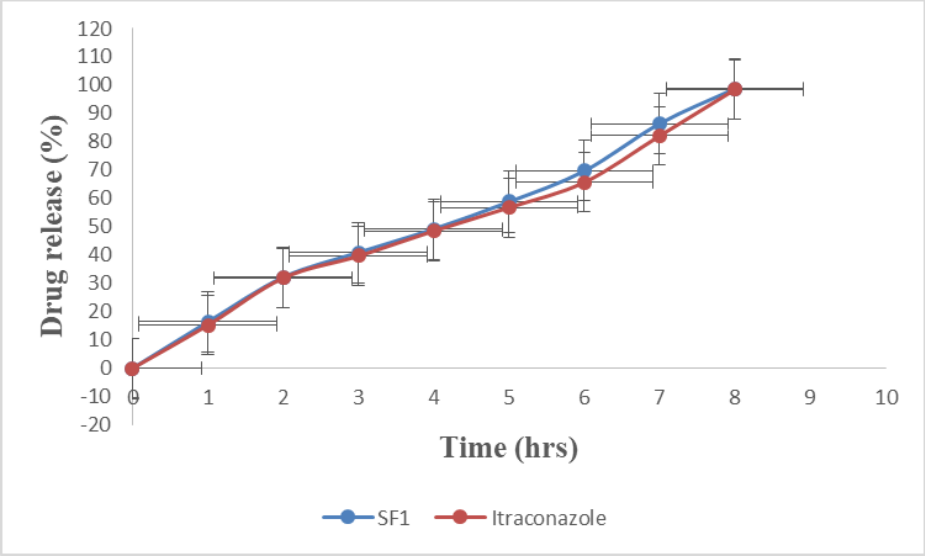


Figure 1 : Drug release of SF1 and Marketed formulation (ITZ).

Conclusion –

The in vitro dissolution study comparing SF1 with the marketed formulation indicates a similar drug release pattern over time. Both formulations exhibit a gradual increase in drug release, with SF1 consistently showing slightly higher release percentages at each time point. At the 8-hour mark, SF1 achieves 98.82% drug release, slightly higher than the marketed formulation (98.5%),

Suggesting effective drug release. The difference in release rates is more noticeable in the middle time points, where SF1 demonstrates improved release compared to the marketed formulation. These results suggest that SF1 has a comparable or slightly enhanced dissolution profile, which could contribute to improved bioavailability. Overall, SF1 is a promising formulation with efficient drug release, making it a potential alternative to the marketed product.

Kinetic analysis of drug release-

In order to define the release mechanism that gives the best description of the release pattern; the in vitro release data for all optimized batches were fitted to kinetic equations models. The kinetic equations were used i.e., zero, first-order and Higuchi model. Both the kinetic rate constant (k) and the determination coefficient (R2) were calculated and presented in below graphs. The best fit model with the highest determination coefficient (R2) value for optimized batch (SF1) was Zero order model.

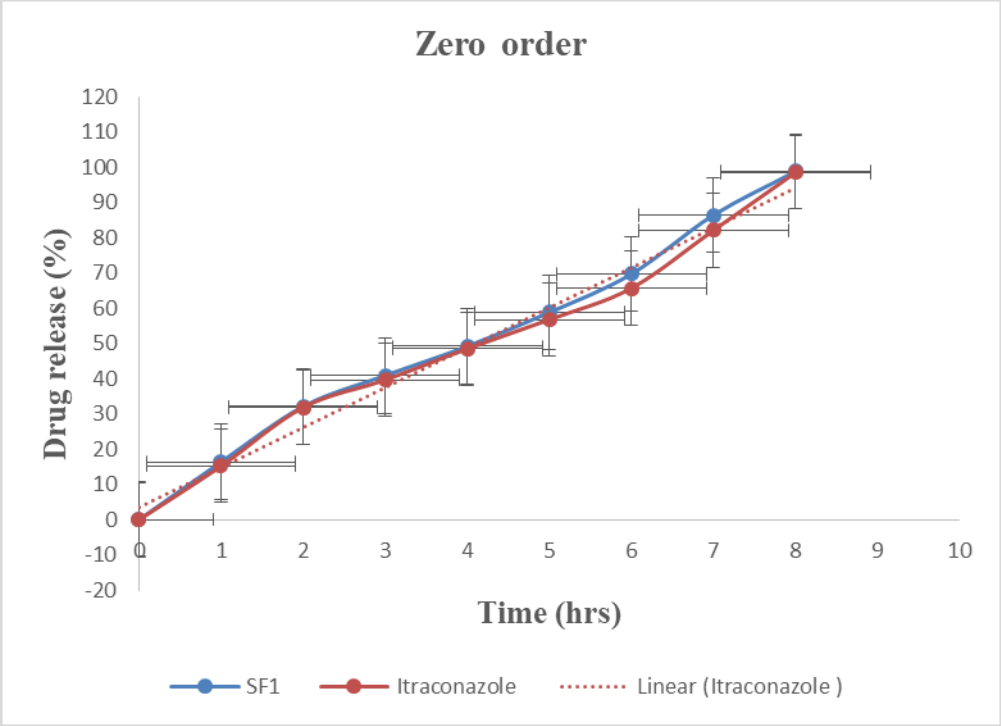


Figure 2: Zero order of SF1 and ITZ.

Table 6: Zero order of SF1 and ITZ.

ZERO ORDER MODEL	
Formulation Code	**R2 Value**
SF1	0.9906
ITZ	0.9854

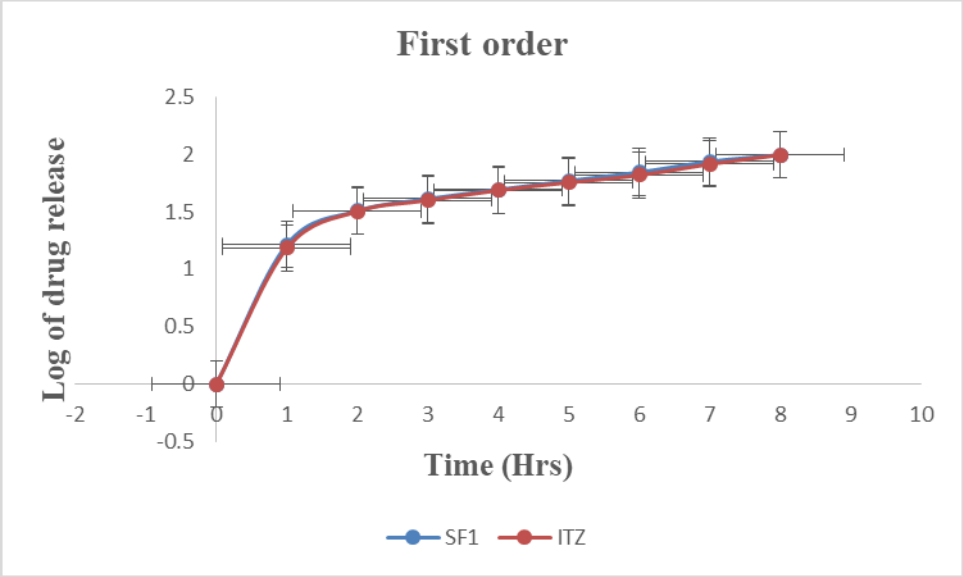


Figure 3: First order of SF1 and ITZ.

Table 7: First order of SF1 and ITZ.

FIRST ORDER MODEL	
Formulation Code	**R2 Value**
SF1	0.6678
ITZ	0.672

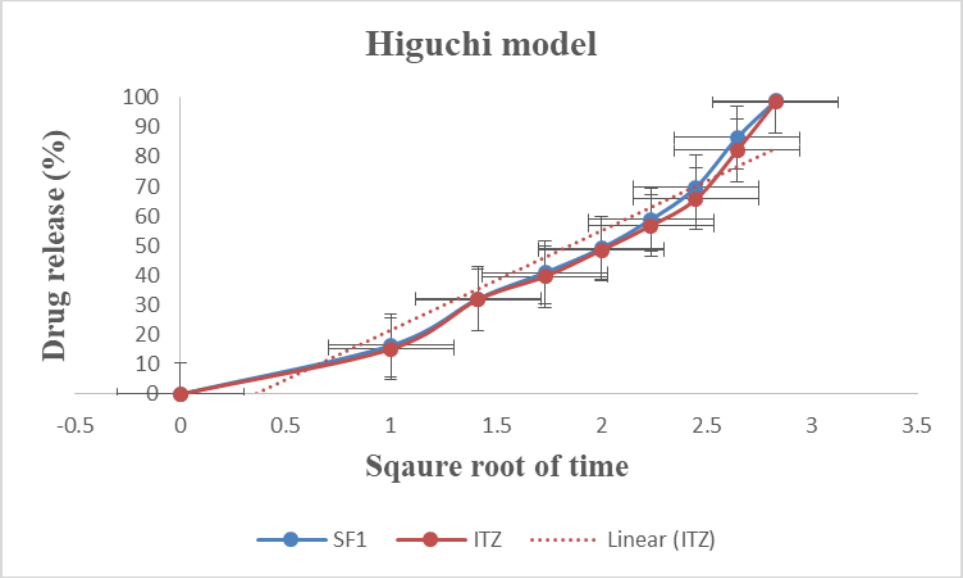


Figure 4: Higuchi model of SF1 and ITZ.

Table 8: Higuchi model of SF1 and ITZ.

HIGUCHI MODEL	
Formulation Code	**R2 Value**

SF1	0.9288
ITZ	0.9216

3.2.4 Particle Size, PDI and zeta potential

Table 9: Particle Size, PDI and zeta potential of SF1.

Formulation code	Particle size (nm)	PDI	Zeta potential (mV)
SF1	95.2	0.115	-29.3

Conclusion-

The characterization of SF1 demonstrates excellent physicochemical properties with a small particle size (95.2 nm), indicating a potential for enhanced dissolution and bioavailability. The low polydispersity index (PDI = 0.115) suggests a uniform particle distribution, which is essential for formulation stability and reproducibility. Additionally, the high negative zeta potential (-29.3 mV) signifies good colloidal stability, reducing the likelihood of particle aggregation. These characteristics collectively suggest that SF1 is a well-optimized formulation with superior stability and potential for effective drug delivery.

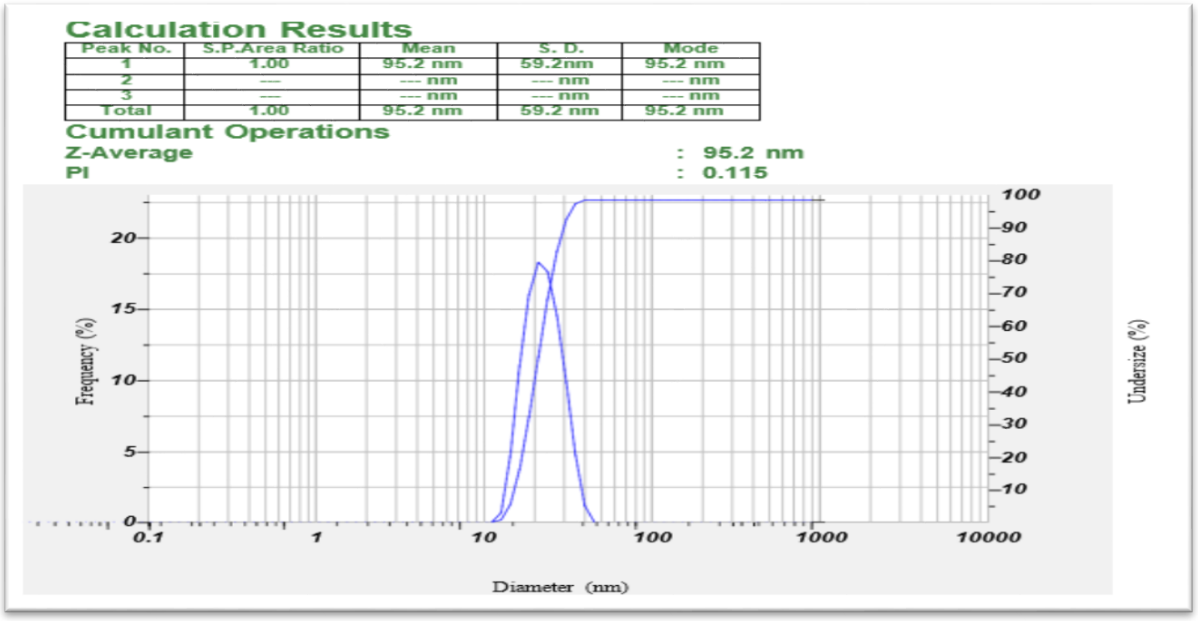


Figure 5: Particle size and PDI of SF1.

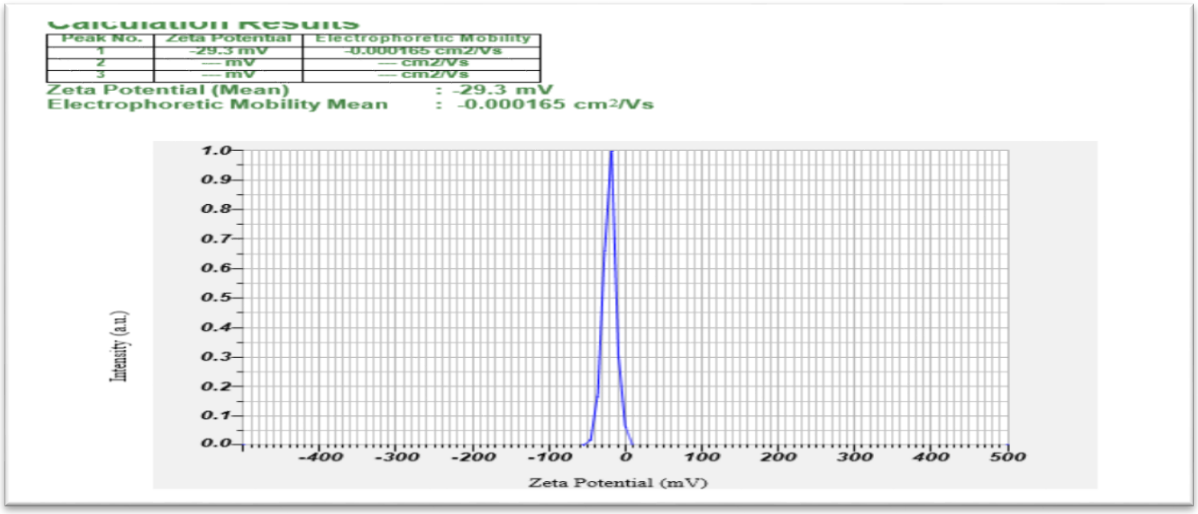


Figure 6: Zeta potential of SF1.

3.2.5 Field Emission Scanning Electron Microscopy (FESEM)

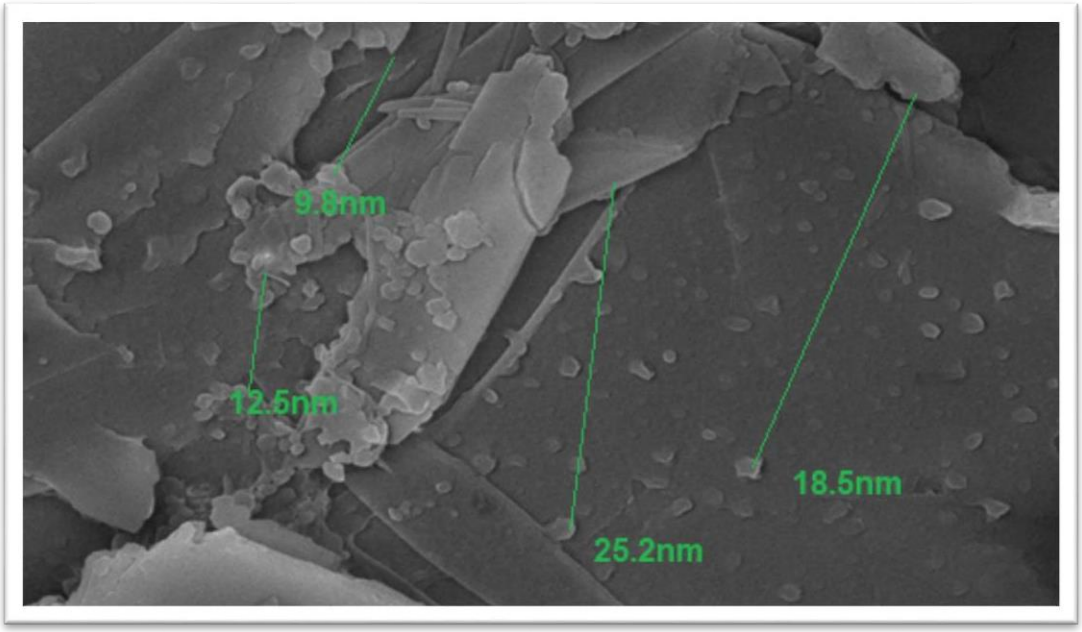


Figure 7: FESEM of SF1.

Conclusion

The FESEM image of SF1 reveals the morphology and particle size distribution of the formulation. The observed nanometer-scale structures (ranging from 9.8 nm to 25.2 nm) confirm the nanosized nature of SF1, which is beneficial for enhancing drug dissolution and bioavailability. The surface appears smooth with some aggregated particles, suggesting good formulation stability. The Presence of uniformly dispersed nanoparticles indicates successful solidification and minimal particle agglomeration. Overall, the FESEM analysis confirms that SF1 exhibits a well-structured, nanosized formulation with favorable surface characteristics for effective drug delivery.

3.2.6 FTIR (Fourier transform infra-red Spectroscopy

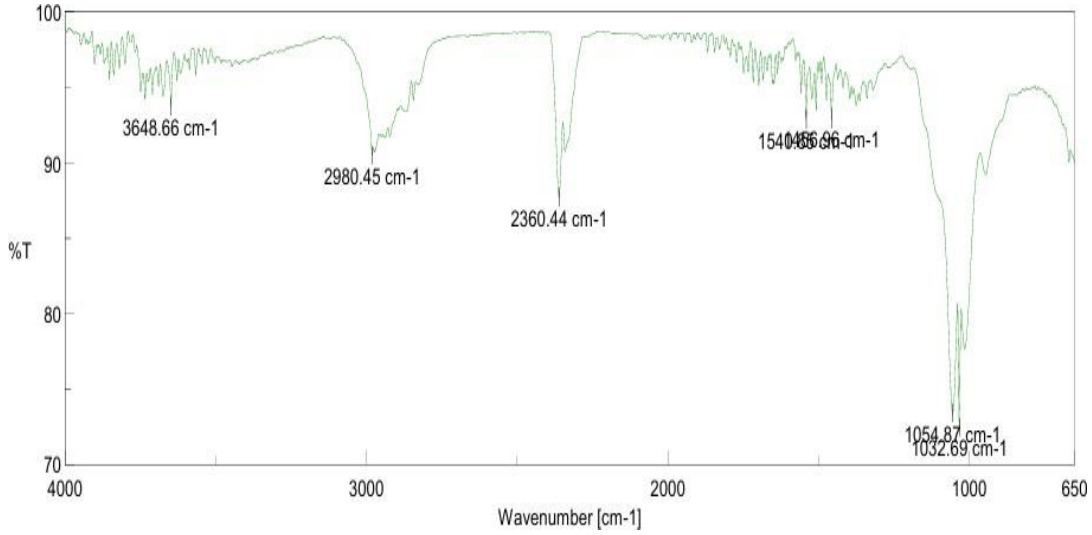


Figure 8: FTIR Spectrum of SF1.

Conclusions

The FTIR interpretation of SF1 confirms the presence of key functional groups, indicating the integrity of the formulation components. The observed O-H stretching at 3648.66 cm^{-1} falls within the reported range, confirming the presence of hydroxyl groups. The C-H aliphatic stretching at 2980.45 cm^{-1} aligns well with the expected range, suggesting the presence of alkane structures. The C≡C or C≡N triple bond stretch appears at 2360.44 cm^{-1}, slightly deviating from the reported range, which may be due to molecular interactions within the formulation. The N-H bending at 1540.65 cm^{-1} and the C-O stretching at 1054.87 cm^{-1} and 1032.69 cm^{-1} confirm the presence of amide and ester/ether groups, respectively. The absence of unexpected peaks suggests no significant chemical interactions or degradation, indicating the stability and compatibility of SF1's components.

3.2.7 Differential scanning calorimetry

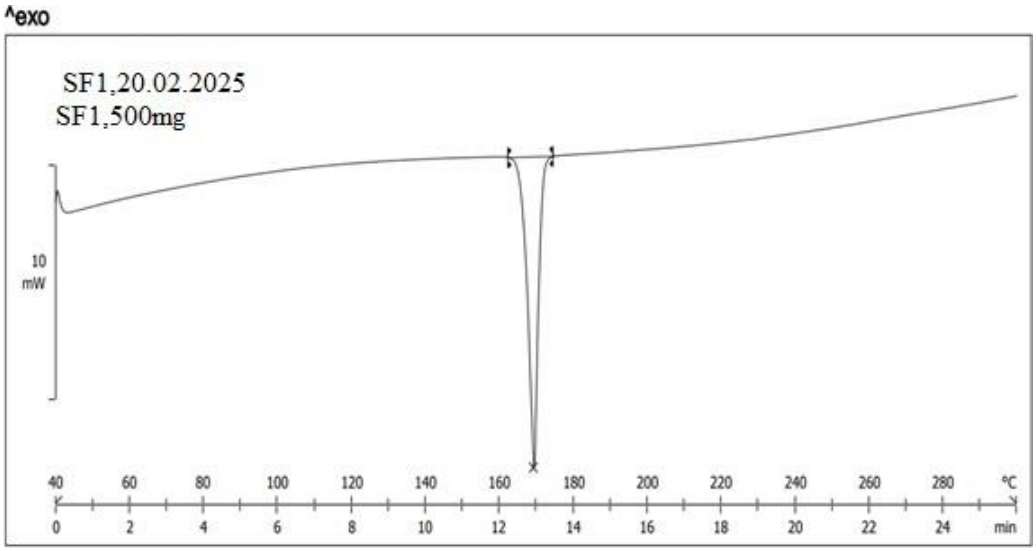


Figure 9: DSC thermogram of SF1.

Conclusions

The DSC thermogram of SF1 exhibits a sharp endothermic peak at 167.2°C, indicating the melting point of the drug or a key excipient. This suggests that the formulation retains its crystalline nature without significant polymorphic transformations or degradation. The absence of additional peaks signifies no major interactions or incompatibilities within the formulation components. This thermal stability further supports the stability study findings, confirming that SF1 remains structurally intact under storage conditions

3.2.8 X-ray Diffraction study

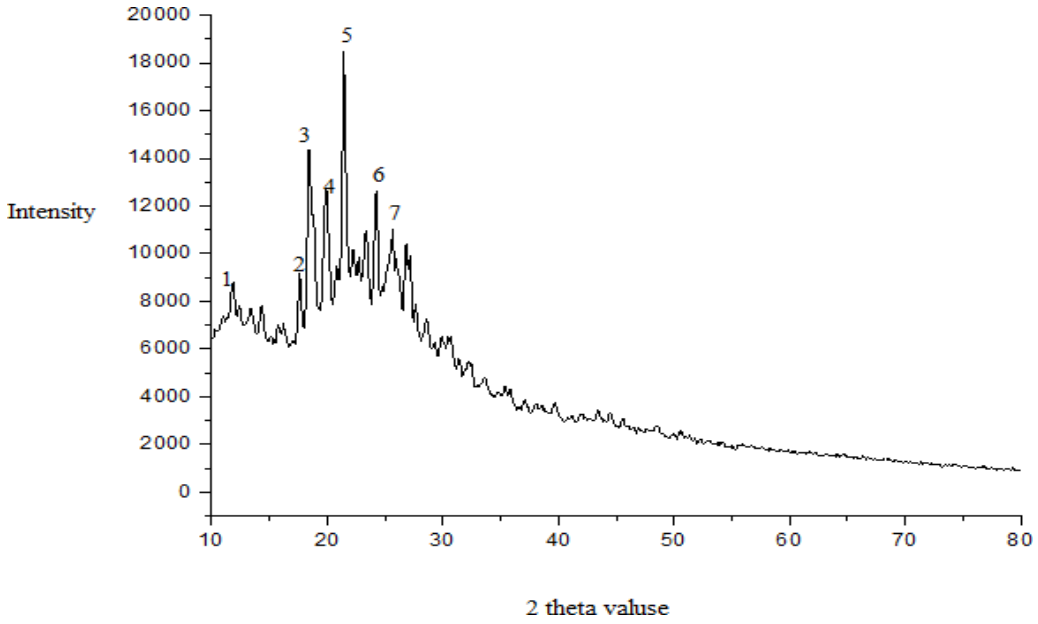


Figure 10: Diffractogram of SF1.

Conclusions

The Diffractogram of Sf1 displays characteristic peaks at 2θ values of 10.2°, 18.9°, 19.81°, 21.0°, 22.3°, 24.5°, and 25.1°. The presence of sharp and intense peaks suggests a crystalline nature of the sample. The highest intensity peak at 22.3° indicates a predominant crystalline phase. Beyond 30°, the intensity decreases, indicating a possible amorphous region. This diffraction pattern confirms the partial crystallinity of the material, which may influence its physicochemical properties such as solubility and stability.

7.3.1.8 Stability Study

Table 10: Stability study of SF1.

Sr.no	Parameter	Initial month	1 Month	2 Month	3 Month
1.	Drug Content (%)	95.15±0.12	95.15±0.12	95.10±0.11	95.11±0.12
2.	Entrapment Efficiency (%)	89.56±0.12	89.56±0.12	89.56±0.11	89.56±0.10
3.	Drug release (%)	98.82±0.12	98.82±0.12	98.80±0.11	98.80±0.11

Conclusions-

The stability study of SF1 was conducted over a period of three months, evaluating key parameters such as drug content, entrapment efficiency, and drug release. The results indicate that there were no significant changes in these parameters over time. The drug content remained consistent, with a slight but negligible variation from 95.15% to 95.11%. Similarly, the entrapment efficiency remained stable at 89.56% throughout the study, suggesting no degradation or leakage of the encapsulated drug. The drug release profile also exhibited minimal variation, maintaining a release percentage of approximately 98.82% across the study period. These findings suggest that SF1 is stable under the tested conditions, ensuring its efficacy and integrity over the studied duration.

Conclusion

The optimized Solid-SNEDDS formulation (SF1) for itraconazole successfully enhanced solubility and oral bioavailability, exhibiting efficient drug loading, high entrapment efficiency, and improved in vitro dissolution compared to the marketed formulation. The formulation demonstrated good colloidal stability, uniform particle size, and maintained stability over three months, making it a promising approach for delivering poorly water-soluble drugs.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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