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ITRACONAZOLE SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEM: A COMPREHENSIVE STUDY ON BCS CLASS II DRUG TRANSFORMATION FOR OPTIMAL ORAL DELIVERY

A COMPREHENSIVE STUDY

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ABSTRACT

Background: Itraconazole, a BCS Class II antifungal agent, exhibits poor water solubility and variable oral bioavailability, limiting its therapeutic efficacy. Self-nanoemulsifying drug delivery systems (SNEDDS) have emerged as an effective strategy for improving drug dissolution and absorption. By enhancing solubility and ensuring rapid drug release, SNEDDS formulations offer a promising alternative to conventional dosage forms. This study focuses on the development and evaluation of an optimized SNEDDS formulation for itraconazole to improve its oral bioavailability and therapeutic potential.

Objective: This study aimed to formulate and characterize an optimized SNEDDS for itraconazole, ensuring improved solubility, stability, and dissolution performance compared to conventional formulations.

Methods: Pseudo-ternary phase diagrams were employed to optimize the formulation, selecting oleic acid as the oil phase, Tween 80 as the surfactant, and PEG 200 as the co-surfactant. Twenty-seven formulations were initially prepared, out of which six were shortlisted based on isotropic properties. Formulations underwent rigorous characterization, including visual inspection, thermodynamic stability studies, freeze-thaw cycling, centrifugation tests, self-emulsification time analysis, cloud point determination, robustness to dilution, and Fourier Transform Infrared (FTIR) spectroscopy. In vitro drug release was evaluated using a USP Type II dissolution apparatus.

Results: Among the formulations, IT3 exhibited the highest stability and optimal self-emulsification, achieving complete dissolution in 180 minutes. Other formulations demonstrated drug release in 240 to 360 minutes, while the commercial Sporanox capsule released only 67% of the drug after 600 minutes. Thermodynamic studies confirmed that IT3 was the most stable, receiving an "excellent" rating, while IT4 and IT6 were classified as "good." Cloud point analysis showed stability up to 80°C, and robustness to dilution studies confirmed no phase separation even after 1000-fold dilution. FTIR spectroscopy confirmed compatibility between itraconazole and formulation excipients.

Conclusion: The optimized SNEDDS formulation significantly improved the solubility and dissolution rate of itraconazole, outperforming conventional dosage forms. The study highlights the potential of SNEDDS as an effective oral drug delivery strategy for poorly soluble drugs, providing a robust formulation approach for enhanced therapeutic efficacy.

Keywords: Bioavailability, Dissolution, Itraconazole, Nanoemulsion, Self-nanoemulsifying drug delivery system, Solubility, Stability.

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INTRODUCTION

Itraconazole, a widely used antifungal agent, presents a significant challenge in oral drug delivery due to its poor water solubility and low bioavailability. Despite the oral route being the most convenient, safest, and cost-effective method of drug administration, its success largely depends on the solubility and permeability of the active pharmaceutical ingredient (1). The Biopharmaceutical Classification System (BCS) categorizes drugs based on these properties, and BCS Class II drugs, such as itraconazole, are characterized by low solubility but high permeability. The primary limitation in their therapeutic effectiveness lies in their dissolution rate, which serves as a key determinant of bioavailability and subsequent pharmacological action (2). Pharmaceutical companies continuously explore innovative drug delivery strategies to enhance the dissolution of poorly soluble drugs. Traditional approaches, including micronization and solid dispersion techniques, have demonstrated limited success in addressing the solubility issues associated with lipophilic drugs (3). Lipid-based formulations, particularly self-nanoemulsifying drug delivery systems (SNEDDS), have emerged as a promising strategy to enhance drug solubilization and absorption. These isotropic mixtures of oil, surfactants, co-surfactants, and drug components spontaneously form nano-sized emulsions in the gastrointestinal tract, thereby increasing drug dissolution and facilitating its systemic absorption (4). The amphiphilic nature of artificial oils, surfactants, and co-surfactants has been found to offer superior solubilization compared to plant-based oils, further enhancing drug release kinetics (5).

Itraconazole, when administered conventionally, exhibits highly variable bioavailability and demonstrates improved absorption when taken with food. To overcome these limitations, self-emulsifying formulations have been explored to improve its pharmacokinetic profile. The Hydrophilic-Lipophilic Balance (HLB) method has been introduced as a novel formulation strategy, ensuring enhanced bioavailability through rapid and complete drug release within 3 to 6 hours (6). While prior studies have highlighted the advantages of SNEDDS for itraconazole, further investigation into formulation optimization and characterization remains necessary to establish a standardized and clinically viable drug delivery system (7). This study aims to develop and characterize an optimized SNEDDS formulation for itraconazole using the HLB method, with the objective of improving dissolution rates and oral bioavailability. By addressing the solubility challenges associated with itraconazole, this research contributes to expanding formulation options for clinicians and patients, offering a more effective and reliable oral drug delivery approach (8).

METHODS

This study was designed to develop and evaluate a self-nanoemulsifying drug delivery system (SNEDDS) for itraconazole using the Hydrophilic-Lipophilic Balance (HLB) method to enhance oral bioavailability. The methodology comprised a series of systematic investigations, including drug solubility assessments, formulation optimization, phase diagram construction, preparation of SNEDDS, and various physicochemical evaluations. Ethical approval for this research was obtained from the Institutional Review Board (IRB) or Ethical Committee, ensuring compliance with ethical guidelines. Itraconazole was obtained from Ferozsons Laboratories Limited, Lahore, Pakistan. Oleic acid, used as the oil phase, was sourced from The Islamia University of Bahawalpur, Punjab, Pakistan. The surfactant Tween 80 was procured from BDH Laboratories Ltd, United Kingdom, while the co-surfactants PEG 200 (poly-oxyethylene 200) and PEG 400 were sourced from Avonchem, UK. Additionally, Tween 20 and Span 20 were obtained from BDH Laboratories, UK, and Sigma Aldrich, Germany, respectively.

Drug Solubility Studies

Given the hydrophobic nature and ionization behavior of itraconazole at low pH, its solubility was assessed in different excipients, including oils (oleic acid, coconut oil, corn oil, castor oil, cottonseed oil, sweet almond oil, sesame oil, olive oil), surfactants (Tween 80, Tween 60, Tween 20, Span 80, Span 20), and co-surfactants (propylene glycol, PEG 200, PEG 400). Excess itraconazole was added to 2 mL of each vehicle and incubated at 50°C for 40–45 minutes. Samples were centrifuged at 10,000 rpm for 10 minutes to remove undissolved drug particles, and the supernatant was diluted with methanol before UV-visible spectrophotometric analysis. A blank solution was used to deduct absorbance interference. The excipients demonstrating maximum solubility for itraconazole were oleic acid (oil vehicle), Tween 80 (surfactant), and PEG 200 (co-surfactant), with complete mutual solubility (9).

Screening of Surfactants and Co-Surfactants

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Surfactants and co-surfactants, including Tween 80, Tween 20, propylene glycol, PEG 200, Span 20, Span 80, and PEG 400, were screened for their ability to form stable emulsions. Various concentrations were altered to achieve different HLB values. The oil-surfactant-co-surfactant mixtures underwent magnetic stirring for six hours, followed by observation for phase separation. The most stable formulations were subjected to self-emulsification tests. The screening process consisted of three phases:

1. **Oil phase variation** – Altering oil percentage and selecting the formulation with optimal physical characteristics.
2. **Surfactant/co-surfactant variation** – Adjusting concentrations based on pre-defined criteria.
3. **Drug loading capacity** – Optimizing the formulation for maximum drug solubilization.

The resultant isotropic mixtures were evaluated for their spontaneous nanoemulsion-forming ability.

Construction of Pseudo-Ternary Phase Diagram

To optimize the SNEDDS formulation, pseudo-ternary phase diagrams were constructed. Based on the solubility study, oleic acid was chosen as the oil phase, Tween-80 (HLB 15) as the surfactant, and PEG 200 (HLB 5) as the co-surfactant. Distilled water was used as the aqueous phase. Surfactant and co-surfactant mixtures (Smix) were prepared at weight ratios of 2:1, 1:1, and 1:2. Oil and Smix combinations were systematically tested at weight ratios ranging from 1:9 to 1:1. The phase behavior of nanoemulsions was examined using spontaneous emulsification, evaluating transparency and flowability. A pseudo-three-component phase diagram was constructed to visually represent the physical state of the nanoemulsions.

Preparation of SNEDDS Using HLB Method

Formulations were prepared using the HLB method, ensuring a stable self-nanoemulsifying system. A combination of surfactants with varying HLB values was explored to optimize stability and emulsification properties. Tween 80 (HLB 15) was selected as the primary surfactant due to its inhibitory effects on P-glycoproteins and cytochrome enzymes, while PEG 200 (HLB 5) was used as a co-surfactant. Various surfactant and co-surfactant ratios were tested, leading to 11 distinct formulations with HLB values ranging from 5 to 15. Formulations with an HLB value of 10 or higher demonstrated optimal stability and self-emulsification, whereas lower HLB combinations resulted in phase separation or poor emulsification (10).

Evaluation of SNEDDS

To assess formulation stability and self-emulsification efficiency, the following evaluations were conducted:

- **Thermodynamic Stability Studies** – Formulations were subjected to refrigeration at 4°C and heating at 45°C in an incubator. Those that remained stable proceeded to freeze-thaw cycling.
- **Freeze-Thaw Cycles** – Three cycles between -21°C and 25°C, each lasting 48 hours, were conducted to assess formulation integrity under extreme conditions.
- **Centrifugation Test** – Samples were diluted 100-fold with distilled water and centrifuged at 3000 rpm for 30 minutes to evaluate phase separation.
- **Self-Emulsification Time** – Formulations were assessed for their ability to emulsify rapidly under mild agitation.
- **Cloud Point Measurement** – SNEDDS formulations were diluted 100-fold and heated in a water bath. The cloud point was recorded as the temperature at which the formulation turned turbid.
- **Robustness to Dilution** – Stability was evaluated after diluting formulations 50-, 100-, and 1000-fold in different dissolution media (distilled water and pH 6.8 buffer) and storing them for 12 hours to check for phase separation or drug precipitation.

Fourier Transform Infrared (FTIR) Spectroscopy

Fourier-transform infrared spectroscopy (FTIR) was employed to evaluate potential chemical interactions between itraconazole and formulation excipients. Samples, including itraconazole, Tween 80, PEG 200, oleic acid, and formulation IT3, were analyzed within the spectral range of 4500–450 cm^{-1}.

In Vitro Drug Release Studies

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The in vitro drug release of SNEDDS formulations was assessed using a USP Type II dissolution apparatus (paddle method) (Pharma test W00 4895, Hainburg, Germany). A dialysis membrane was pre-soaked in dissolution media for 24 hours before testing. SNEDDS formulations, equivalent to 5 mg of itraconazole, were placed in 900 mL of phosphate buffer (pH 6.8) maintained at 37 ± 2°C with a stirring speed of 50 rpm. Samples (5 mL) were withdrawn at predefined intervals (5, 10, 15, 30, 45, 60, 120, 180, 240, 300, 360, 480, 600, and 720 minutes) and replaced with an equal volume of fresh dissolution medium. The samples were filtered and analyzed using a UV-visible spectrophotometer (IRMACO GmbH, Geesthacht, Germany) at 262 nm, as determined by a previously established calibration curve. The release profiles of SNEDDS, a commercial itraconazole tablet, and the pure drug (active pharmaceutical ingredient, API) were analyzed using DD Solver.xla software.

Table 1: Composition of SNEDDS formulation

Formulation	Smix ratio	O: Smix
IT_1	2:1	1:9
IT_2	2:1	1:8
IT_3	2:1	1:7
IT_4	2:1	1:6
IT_5	2:1	1:5
IT_6	2:1	1:4
IT_7	2:1	1:3
IT_8	2:1	1:2
IT_9	2:1	1:1
IT_{10}	1:1	1:9
IT_{11}	1:1	1:8
IT_{12}	1:1	1:7
IT_{13}	1:1	1:6
IT_{14}	1:1	1:5
IT_{15}	1:1	1:4
IT_{16}	1:1	1:3
IT_{17}	1:1	1:2
IT_{18}	1:1	1:1
IT_{19}	1:2	1:9
IT_{20}	1:2	1:8
IT_{21}	1:2	1:7
IT_{22}	1:2	1:6
IT_{23}	1:2	1:5
IT_{24}	1:2	1:4

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Formulation	Smix ratio	O: Smix
IT_{25}	1:2	1:3
IT_{26}	1:2	1:2
IT_{27}	1:2	1:1

Table 2: HLB values ranging from 5 to 15, resulting in 11 distinct combinations

Sr. No.	HLB value	Tween 80 %	PEG 200 %
1	5	0	100
2	6	10	90
3	7	20	80
4	8	30	70
5	9	40	60
6	10	50	50
7	11	60	40
8	12	70	30
9	13	80	20
10	14	90	10
11	15	100	0

RESULTS

The UV spectroscopic method exhibited a linear standard curve for itraconazole within the concentration range of 2–14 µg/mL. The absorbance values demonstrated a proportional increase with increasing drug concentration, confirming the reliability of the calibration curve for subsequent analyses. Solubility studies indicated that itraconazole displayed the highest solubility in oleic acid (73.55 ± 1.22 mg/mL) among the tested oils, while cottonseed oil exhibited the lowest solubility (17.93 ± 0.51 mg/mL). Among surfactants, Tween 80 exhibited the maximum solubility (21.09 ± 1.73 mg/mL), whereas Span 20 showed the lowest solubility (8.73 ± 0.82 mg/mL). Polyethylene glycol 200 (PEG 200) demonstrated the highest solubility (31.04 ± 0.88 mg/mL) among co-surfactants, while propylene glycol had the lowest solubility (23.25 ± 1.49 mg/mL). Based on these findings, oleic acid, Tween 80, and PEG 200 were selected as the oil phase, surfactant, and co-surfactant, respectively, for further formulation development.

Pseudo-ternary phase diagram studies revealed that nanoemulsion formation was significantly influenced by the Smix ratio. Increasing the surfactant-to-co-surfactant ratio (from 1:2 to 2:1) expanded the nanoemulsion region, with the optimal nanoemulsion stability observed at a Smix ratio of 2:1. Conversely, formulations with Smix 1:2 exhibited phase separation within 24 hours. Further increases in PEG 200 concentration did not enhance nanoemulsion stability, confirming the necessity of an optimal surfactant concentration. Itraconazole-loaded SNEDDS formulations were prepared using the selected excipients and characterized for their physicochemical properties. Scanning electron microscopy (SEM) analysis revealed that the nanoemulsion droplets had a smooth, spherical morphology with a geometric diameter of <100 nm, confirming the successful formation of nanoscale dispersions. Visual inspection of the formulations indicated uniform emulsions with no visible phase separation.

Thermodynamic stability studies demonstrated that all formulations remained stable under temperature fluctuations, with no evidence of precipitation or phase separation following exposure to refrigeration (4°C) and high-temperature (50°C) conditions. Freeze-thaw

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cycle analysis further confirmed the stability of the formulations, as they retained their emulsion characteristics after three consecutive cycles between -21°C and 25°C. Centrifugation tests performed at 3000 rpm for 30 minutes confirmed that all tested formulations remained stable without any signs of phase separation. Self-emulsification time assessments indicated that the SNEDDS formulations rapidly dispersed upon mild agitation, with emulsification times ranging from 1 to 2 minutes.

Cloud point measurements showed that all formulations exhibited a clouding effect at temperatures between 70°C and 80°C, demonstrating their thermal stability. Robustness to dilution tests revealed that SNEDDS formulations maintained their structural integrity when diluted at 50-, 100-, and 1000-fold in both distilled water and pH 6.8 buffer, without any precipitation or separation. Fourier-transform infrared (FTIR) spectroscopy analysis confirmed the compatibility of itraconazole with formulation excipients, as no significant shifts or additional peaks were observed in the infrared spectra, indicating the absence of drug-excipient interactions.

In vitro drug release studies demonstrated that the optimized SNEDDS formulations exhibited significantly improved dissolution profiles compared to the commercial tablet formulation. The cumulative drug release from SNEDDS formulations was substantially higher, with IT1 achieving 98.7% drug release within 180 minutes, IT3 reaching 99.5% in 180 minutes, and IT5 attaining 99.4% in 360 minutes. In contrast, the commercial itraconazole tablet exhibited a cumulative release of only 66.98% after 600 minutes. These findings highlight the potential of SNEDDS in enhancing the dissolution and bioavailability of itraconazole.

Table 3: Known concentrations of itraconazole and their absorbance

Sr. No.	Concentration (µg/ml)	Absorbance (nm)
1	2	0.106 ±0.0073
2	4	0.212 ±0.0017
3	6	0.284 ±0.0023
4	8	0.383 ±0.0015
5	10	0.466 ±0.0026
6	12	0.576 ±0.0044
7	14	0.632 ±0.0060

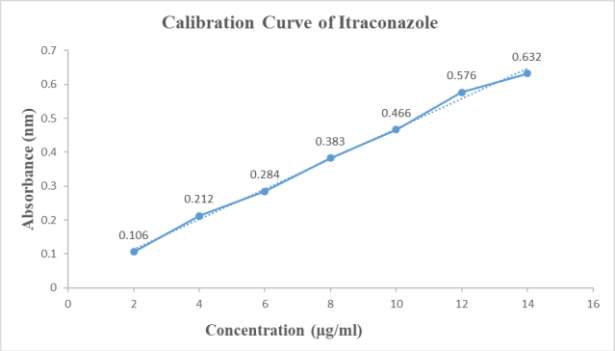
Table 4: Solubility of itraconazole in different oils, surfactants and cosurfactants (mean ±SD, n=3)

	Solubility-(mg/ml)
Oils	
Oleic acid	73.55±1.22
Coconut oil	47.09±0.33
Corn oil	33.12±0.19
Castor oil	25.38±1.17
Cotton-seed oil	17.93±0.51
Sweet-almond oil	28.72±1.44
Sesame oil	19.64±1.83
Virgin olive oil	29.84±0.60
Surfactants	

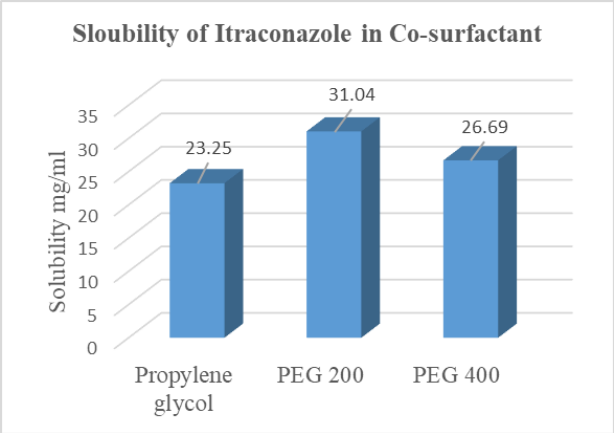
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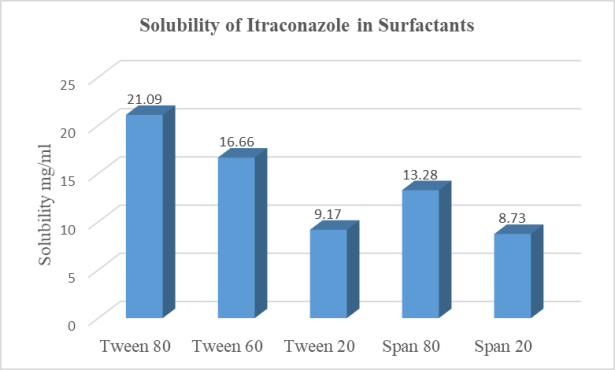
	Solubility-(mg/ml)
Tween-80	21.09±1.73
Tween-60	16.66±0.05
Tween-20	09.17±1.59
Span-80	13.28±0.51
Span-20	08.73±0.82
Cosurfactants	
Propylene glycol	23.25±1.49
PEG 200	31.04±0.88
PEG 400	26.69±1.19



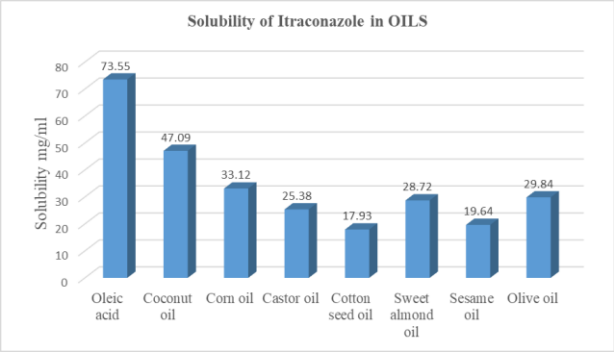
Calibration curve of itraconazole



Sloubility of Itraconazole in Co-surfactant



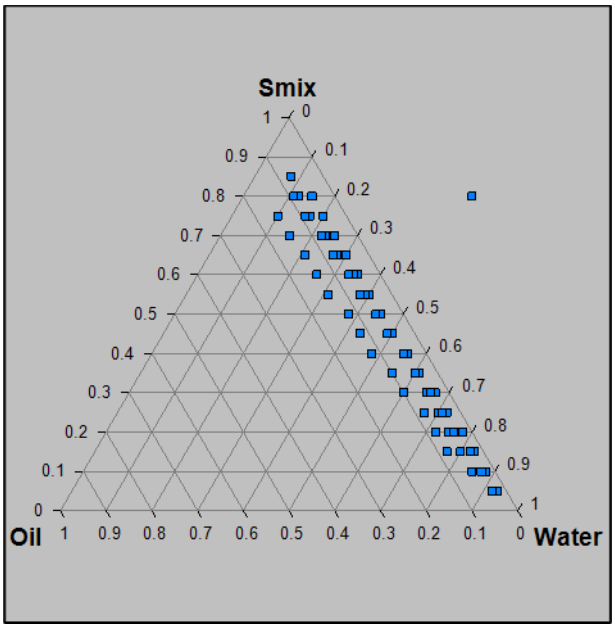
solubility of itraconazole in surfactants



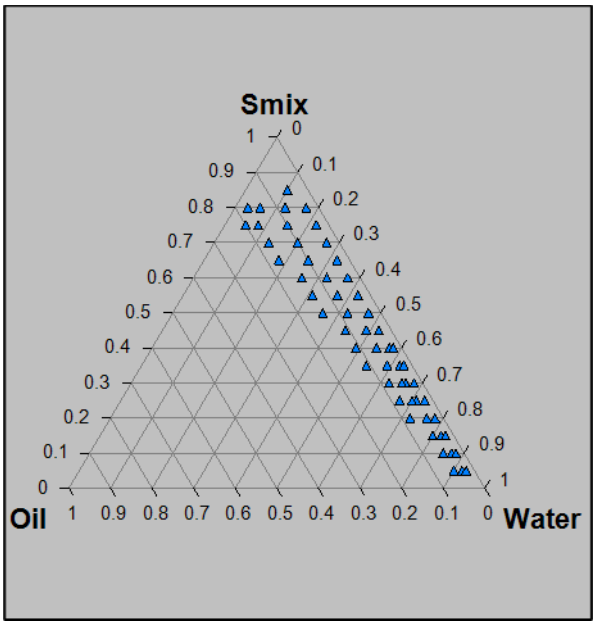
Solubility of itraconazole in different oils

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A.Phase diagram of Smix ratio 1:1



B. Phase diagram of Smix ratio 2:1

Table 5: Formulation after visual inspection were rated according to the scale

××××× as excellent, ×××× as good, ××× as fair, ×× average, × as pass and - as fail.

Formulation	Low temperature	High temperature	Eye inspection	Results
IT_1	4°C	50°C	×××	Stable
IT_2	4°C	50°C	×××	Stable
IT_3	4°C	50°C	×××××	Stable
IT_4	4°C	50°C	××××	Stable
IT_5	4°C	50°C	×××	Stable
IT_6	4°C	50°C	××××	Stable

Table 6: Formulations passed through Freeze-thaw cycle

Formulation	Less temperature	High temperature	Eye inspection	Results
IT_1	4°C	50°C	×××	Stable
IT_2	4°C	50°C	×××	Stable
IT_3	4°C	50°C	××××	Stable
–			×××	Stable
IT_5	4°C	50°C	××	Stable
IT_6	4°C	50°C	×××	Stable

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Table 7: Centrifugation test of formulations

Formulation	Centrifuge speed & time	Result
IT_1	3000 rpm – 30 min	Stable
IT_2	3000 rpm – 30 min	Stable
IT_3	3000 rpm – 30 min	Stable
IT_4	3000 rpm – 30 min	Stable
IT_5	3000 rpm – 30 min	Stable
IT_6	3000 rpm – 30 min	Stable

Table 8: Self-emulsification time of final formulations

Formulation	Self-emulsification time	Visual Inspection	Result
IT_1	1.5 minutes	×××	Emulsion formed
IT_2	1.5 minutes	×××	Emulsion formed
IT_3	1 minutes	××××	Emulsion formed
IT_4	2 minutes	××	Emulsion formed
IT_5	1.5 minutes	×××	Emulsion formed
IT_6	2 minutes	××	Emulsion formed

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Table 9: Self-emulsification time of final formulations

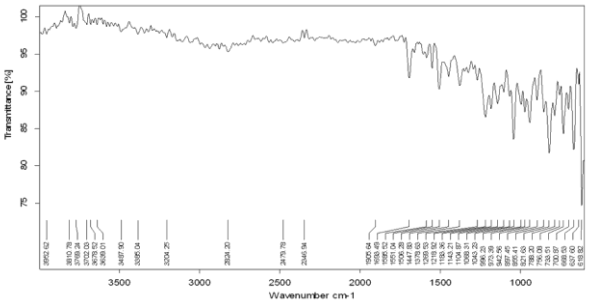
Formulation	Temp. ºC	Appearance	Result
IT_1	70°C	Cloudy	Passed
IT_2	75°C	Cloudy	Passed
IT_3	80°C	Cloudy	Passed
IT_4	75°C	Cloudy	Passed
IT_5	70°C	Cloudy	Passed
IT_6	70°C	Cloudy	Passed

Table 10: The robustness to dilution of Itraconazole SNEDDS

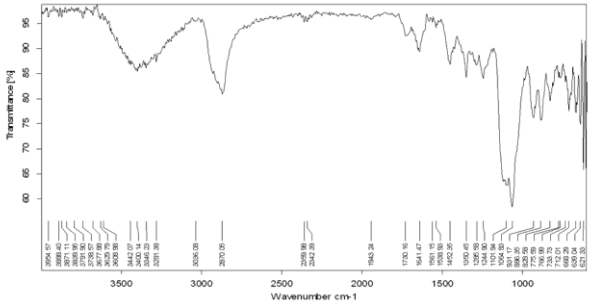
Formulation	Dilution factor	Water of pH 7	Buffer of pH 6.8
IT_1	50 times	×××	××××
	100 times	××	×××
	1000 times	××	×××
IT_2	50 times	×××	××××
	100 times	×××	×××
	1000 times	××	×××
IT_3	50 times	××××	××××
	100 times	×××	××××
	1000 times	××	×××
IT_4	50 times	××	×××
	100 times	×	××
	1000 times	×	×
IT_5	50 times	×××	×××
	100 times	××	××
	1000 times	×	××
IT_6	50 times	×××	×××3
	100 times	××	××
	1000 times	×	××

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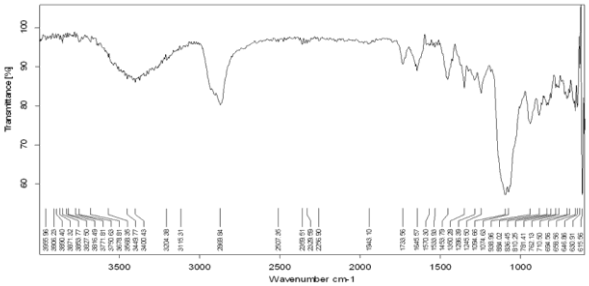
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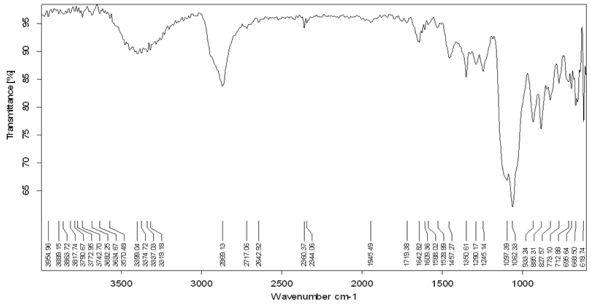
FTIR of pure drug Itraconazole



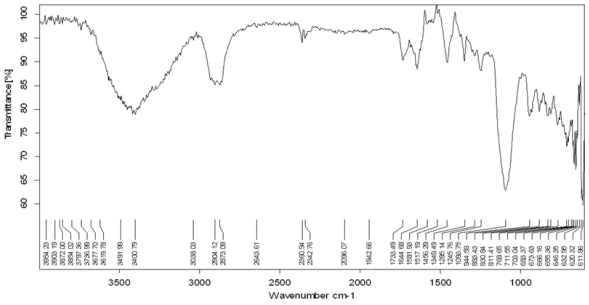
FTIR of Oil (Oleic acid)



FTIR of Surfactant (tween 80)



FTIR of Co-surfactant (PEG 200)



FTIR of Formulation IT3

Table 11: The % release of IT1 is provided below

Sr. No.	Time (min)	%age cumulative release
1	0	0
2	5	11.432
3	10	19.044
4	15	21.809
5	30	24.960
6	45	35.072
7	60	47.657
8	120	75.019
9	180	98.705

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Table 12: % release of IT_2 is given bellow

Sr. No.	Time (min)	%age cumulative release
1	0	0
2	5	10.437
3	10	17.810
4	15	26.581
5	30	30.889
6	45	39.417
7	60	45.110
8	120	56.461
9	180	79.201
10	240	99.590

Table 13:%age cumulative release

Sr. No.	Time (min)	%age cumulative release
1	0	0
2	5	9.825
3	10	16.620
4	15	23.029
5	30	32.481
6	45	42.359
7	60	62.101
8	120	86.904
9	180	99.509

Table 14: % release of IT_4 is given bellow

Sr. No.	Time (min)	%age cumulative release
1	0	0
2	5	9.865
3	10	15.418
4	15	19.909
5	30	26.104
6	45	34.630

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Sr. No.	Time (min)	%age cumulative release
7	60	45.825
8	120	61.954
9	180	72.200
10	240	91.032
11	300	99.879

Table 15: % release of IT_5 is given bellow

Sr. No.	Time (min)	%age cumulative release
1	0	0
2	5	6.790
3	10	9.012
4	15	13.605
5	30	18.534
6	45	23.112
7	60	28.854
8	120	38.377
9	180	49.262
10	240	72.552
11	300	83.196
12	360	99.428

Table 16: % release of IT_6 is given bellow

Sr. No.	Time (min)	%age cumulative release
1	0	0
2	5	3.102
3	10	6.430
4	15	11.622
5	30	19.425
6	45	30.756
7	60	34.832
8	120	42.896
9	180	55.698

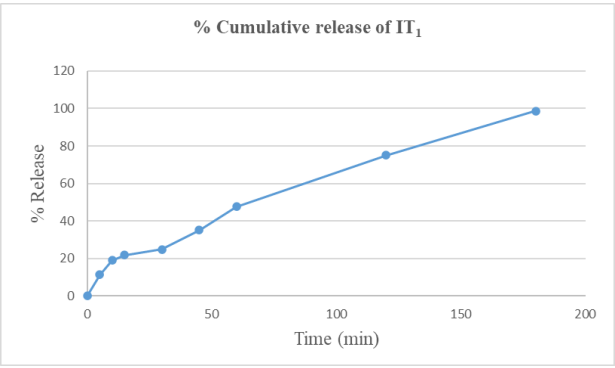
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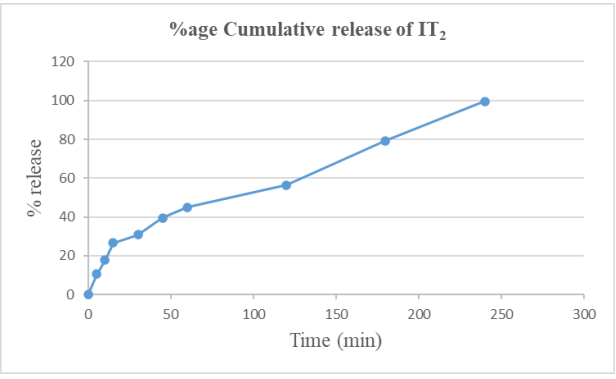
Sr. No.	Time (min)	%age cumulative release
10	240	77.590
11	300	92.175
12	360	99.790

Table 17: % release of commercial tablet is given bellow

Sr. No.	Time (min)	%age cumulative release
1	0	0
2	5	3.102
3	10	11.602
4	15	18.831
5	30	21.368
6	45	29.671
7	60	33.232
8	120	38.228
9	180	44.367
10	240	48.656
11	300	52.505
12	360	56.221
13	480	61.762
14	600	66.980



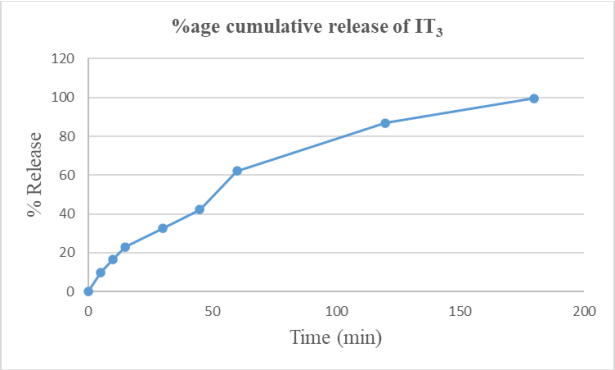
% cumulative release of IT1



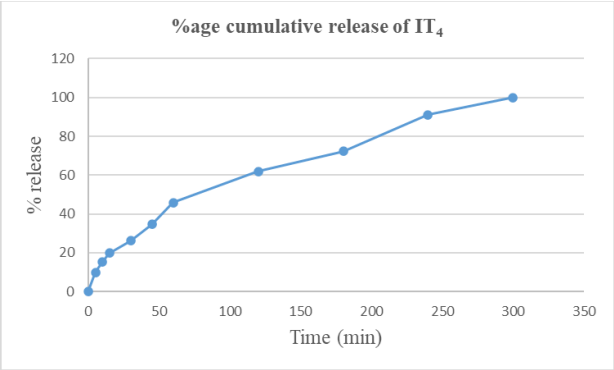
% release of IT3 is given below.

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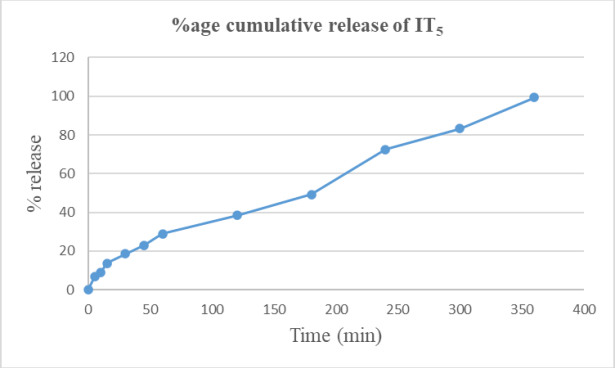
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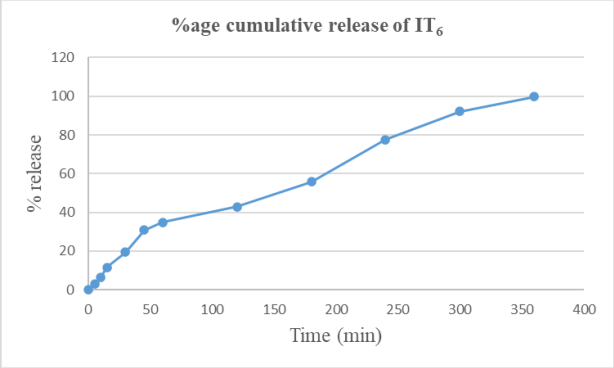
%age cumulative release of IT3



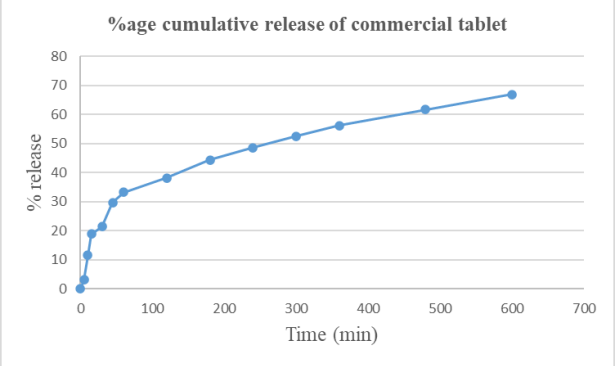
%age cumulative release of IT4



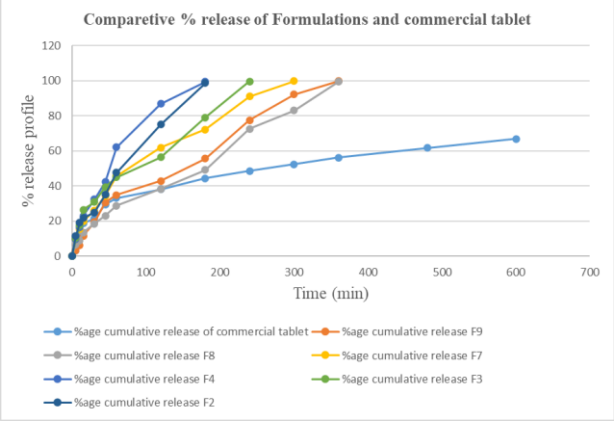
%age cumulative release of IT5



%age cumulative release of IT6



%age cumulative release of commercial tablet



Comparetive % release of Formulations and commercial tablet

DISCUSSION

The development of itraconazole-loaded self-nanoemulsifying drug delivery systems (SNEDDS) demonstrated significant potential for improving drug solubility and bioavailability. The selection of oleic acid, Tween 80, and PEG 200 as the oil phase, surfactant, and co-surfactant, respectively, was supported by solubility studies, aligning with prior research emphasizing the importance of lipid-based formulations for enhancing poorly soluble drugs. Among the 27 formulations initially developed based on the pseudo-ternary phase diagram, only six met the criteria for isotropic stability, highlighting the necessity of optimizing the oil-to-surfactant ratio to ensure formulation homogeneity and prevent phase separation. The exclusion of unstable formulations from further characterization reinforced

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the importance of rigorous screening in formulation development. Thermodynamic stability evaluations confirmed that the selected formulations exhibited resilience under varied temperature conditions. IT3 demonstrated the highest stability, receiving the best rating, whereas other formulations showed moderate stability. These findings were consistent with earlier studies indicating that the hydrophilic-lipophilic balance (HLB) of surfactants plays a critical role in maintaining nanoemulsion stability (11). Freeze-thaw cycling further validated the robustness of the formulations, with IT3 maintaining its integrity across multiple temperature shifts, while others exhibited varying degrees of stability. Such assessments are integral to predicting long-term storage feasibility, a crucial factor in pharmaceutical formulation.

Centrifugation studies provided additional confirmation of the stability of itraconazole SNEDDS, as none of the selected formulations exhibited phase separation. The ability to withstand mechanical stress during dilution is indicative of the robustness of the nanoemulsion system, which is essential for ensuring consistent drug delivery. Self-emulsification efficiency was another determinant of formulation success. IT3 exhibited the shortest emulsification time, suggesting a lower free energy requirement for nanoemulsion formation, a desirable attribute for enhancing drug absorption. The rapid emulsification of IT3 can be attributed to the optimized ratio of surfactant and co-surfactant, which facilitated spontaneous dispersion, as observed in previous studies on lipid-based drug delivery systems (12). Cloud point measurements further confirmed the thermal stability of the formulations, with IT3 remaining stable up to 80°C, while others exhibited clouding at slightly lower temperatures. Since physiological temperature is significantly lower than the threshold values determined in this study, these formulations are expected to maintain their integrity under normal biological conditions. Robustness to dilution was another critical factor, demonstrating that all formulations retained their emulsification properties when diluted in both water and pH 6.8 buffer. The stability of IT3 across multiple dilution factors indicates that the formulation can withstand varying physiological conditions, a key advantage for oral drug delivery.

In vitro drug release studies highlighted the superior dissolution profile of itraconazole SNEDDS compared to conventional capsule formulations. IT3 exhibited the most rapid drug release, reaching complete dissolution within 180 minutes, whereas the commercially available Sporanox capsule released only 67% of the drug after 600 minutes. The enhanced dissolution of SNEDDS formulations can be attributed to the reduction in globule size, which significantly increases surface area and facilitates drug diffusion. The improved release kinetics align with previous research emphasizing the role of nanoemulsification in overcoming solubility-related bioavailability challenges (16). The strengths of this study include the systematic optimization of SNEDDS formulations using phase diagram analysis, thermodynamic evaluations, and dissolution profiling, ensuring a comprehensive assessment of formulation stability and performance. The study successfully demonstrated that a well-balanced ratio of oil, surfactant, and co-surfactant could enhance the solubilization and bioavailability of itraconazole, addressing a major limitation associated with BCS Class II drugs. Additionally, the selection of excipients with established safety profiles supports the feasibility of this formulation for potential clinical translation.

Despite its strengths, certain limitations warrant consideration. The study did not include droplet size distribution, zeta potential, or polydispersity index (PDI) measurements, which are essential for characterizing nanoemulsions in greater detail. The long-term stability of the formulations under storage conditions was not evaluated, which is critical for predicting shelf life. Further in vivo bioavailability studies are required to confirm the pharmacokinetic advantages of SNEDDS over conventional formulations. Additionally, the effect of food on drug absorption was not explored, despite known variations in itraconazole bioavailability when administered with food. Future research should focus on optimizing SNEDDS formulations by incorporating advanced characterization techniques, including dynamic light scattering for droplet size analysis and stability studies under accelerated storage conditions. In vivo pharmacokinetic evaluations should be conducted to determine the bioavailability enhancement achieved through SNEDDS compared to conventional oral dosage forms. Furthermore, exploring the scalability of SNEDDS production and its compatibility with large-scale manufacturing processes will be crucial for clinical translation. The findings of this study reinforce the potential of SNEDDS as a promising strategy for enhancing the oral bioavailability of itraconazole. By addressing solubility limitations, this formulation approach offers a viable alternative to conventional delivery methods, potentially leading to improved therapeutic outcomes for patients requiring antifungal treatment.

CONCLUSION

The development of a self-nanoemulsifying drug delivery system (SNEDDS) for itraconazole successfully addressed the drug's solubility limitations, offering a promising alternative to conventional formulations. Through systematic formulation optimization and comprehensive in vitro evaluations, SNEDDS demonstrated superior dissolution performance and stability, highlighting its potential to enhance oral bioavailability. The findings reinforce the viability of lipid-based nanoemulsions as an effective approach for improving

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drug solubility and absorption, paving the way for better therapeutic outcomes. This study contributes to the advancement of itraconazole delivery, presenting a formulation strategy that could significantly improve patient compliance and treatment efficacy in clinical settings.

Author Contribution

Author	Contribution
Abdul Rauf	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Fahad Pervaiz*	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Hafiz Muhammad Usman Abid*	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Khadija Karim	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Sadia Rehman	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Memoona Qayyum	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Mudassara Liaqat	Contributed to study concept and Data collection Has given Final Approval of the version to be published
Rida Akhtar	Writing - Review & Editing, Assistance with Data Curation
Tahreem Arshad	Writing - Review & Editing, Assistance with Data Curation
Abdul Hassan Khan	Writing - Review & Editing, Assistance with Data Curation

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