RESEARCH ARTICLE

Formulation, Optimization and Evaluation of Solid SMEDDS of Itraconazole in Effervescent Granules Form

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ABSTRACT

This investigation assessed nine formulations of liquid self-micro-emulsifying drug delivery systems (L-SMEDDS) for itraconazole (ITZ). The most effective formulation (ILS_6) consisted of 40% clove as the oil, 40% Kolliphor CS 20 as the surfactant, and 20% polyethylene glycol (PEG) 400 as the co-surfactant. ILS_6 displayed a droplet size of 130 to 165 nm, well below 200 nm, and a polydispersity index (PDI) value of 0.47 to 0.73, indicating the development of an emulsion with nanosized droplets and even spreading. The finalized formulation demonstrated stability under numerous conditions and achieved supreme drug loading capacity. The optimized L-SMEDDS was solidified into solidified SMEDDS (S-SMEDDS) utilizing sylloid 244 FP, resulting in a free-flowing powder without drug interactions. The effervescent system was successfully formulated by incorporating S-SMEDDS with different excipients. The selected effervescent system passed quality control and stability tests. The effervescent system exhibited a rapid and pH-independent release profile. The combined impact of SMEDDS and the effervescent system collectively enhanced the solubility and dissolution of itraconazole.

Keywords: Effervescent solidified SMEDDS, Effervescence time, Itraconazole, Solubility enhancement, Scanning electron microscope, Bioavailability enhancement.

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INTRODUCTION

Oral administration is widely considered the most effective method for numerous drugs, constituting 80% of currently available dosage forms.[1] This preference extends to specific formulations such as controlled, sustained, and fast release, every requiring different formation procedures.[1] The choice of administration route hinges on a thorough investigation and evaluation of the drug's physicochemical properties. Notably, a significant proportion of drugs exhibit low water solubility, with around 68% of oral drugs having poor solubility (< 100 µg/mL). This characteristic leads to inadequate absorption in the stomach environment upon oral intake, resulting in inadequate bioavailability and, therefore, diminished effectiveness.[1]

In the direction of enhancing the solubility of lipophilic drugs with a Log P > 3, lipid-based preparations called self-micro-emulsifying drug delivery systems (SMEDDS) are employed. SMEDDS is a combination of oils and surfactants designed for oral administration.[2] It transforms into a fine emulsion upon ingestion, facilitated by gentle agitation or digestive processes. This emulsion enhances drug absorption, improving bioavailability.[3] SMEDDS formulation improves the absorption of Biopharmeceutical Classification System (BCS) II and IV drugs, enhances dissolution rates, and protects drugs in the gut. It offers stable capsule filling, high drug entrapment, and spontaneous emulsion formation, and it prevents degradation in gastric medium.[4,5]

Itraconazole (ITZ), a triazole derivative, serves as an antifungal agent and falls under the BCS class II because of its lower solubility as well as higher permeability. ITZ is water-insoluble (0.00964 mg/mL), with an absolute bioavailability of 55%, attaining its maximum efficacy when taken with food.[6] Numerous strategies have been explored by investigators in the direction of improving the solubility as well as bioavailability of ITZ, including PLGA nanoparticles, Liquid-SEDDS, mucoadhesive tablets, bioadhesive films, nanoparticles, co-crystals, tablets, crystalline agglomerates, and solid dispersions.[7-10]

SEDDS augment oral bioavailability by keeping drugs in solution in the GIT tract. SMEDDS for ITZ was developed to improve stability over liquid SEDDS. Previous studies showed ITZ SEDDS stability only in acidic conditions with HCl.[11,12] Consequently, this study made efforts to stabilize ITZ without using HCl. Surprisingly, despite an extensive literature search;

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no prior research attempts on effervescent granules SMEDDS of ITZ were identified utilizing routinely used equipment for granulation rather than an expensive spray drying technique.

The aim was to develop an SMEDDS for the poorly water-soluble drug ITZ towards improving its solubility as well as dissolution. Additionally, the study aimed to characterize the resulting SMEDDS thoroughly, concentrating on its physicochemical properties, performance, and stability.

MATERIAL AND METHODS

Materials

Itraconazole, along with numerous oils (e.g., corn oil, castor oil), surfactants (e.g., Span 80, Tween 80), and additives (e.g., Labrafil M 2125, Labrasol) were procured from Sigma Aldrich Pvt. Ltd, New Delhi, India. Additionally, chremophor ELP (Polyoxyl 35 Hydrogenated Castor oil) and chremophor RH40 were supplied by BASF, Mumbai, India. Chemicals were of analytical grade, and double-distilled water was used.

Methods

Solubility study

To assess the solubility characteristics of itraconazole (ITZ) in different oil, surfactant, and co-surfactant vehicles, along with buffers, experiments were conducted through solubilizing an additional quantity of the drug in 2 mL of every medium. The capped cuvettes containing the blends were then positioned in an orbital shaking incubator at 25ºC for 72 hours, with the aid of a vortex mixer if needed to enhance solubilization. Subsequent a 24-hour equilibrium period at ambient temperature, every blend underwent centrifugation at 3000 rpm for 15 minutes. Any un-dissolved ITZ was eliminated and filtered. ITZ concentration was analyzed *via* UV spectroscopy.[13-15]

Emulsification Efficiency Study

Selection of surfactant

The emulsification efficiency of surfactants was tested to identify the best ones for spontaneously emulsifying clove oil, chosen for its ability to solubilize ITZ. The process mirrored that of the solubility studies.[16]

Selection of co-surfactant

The available co-surfactants for oral delivery were partitioned to improve the emulsification capability of designated surfactant Kolliphore CS 20 to emulsify oily phase clove oil (CO). The same experiment was performed as described earlier in solubility studies. On the basis of solubility study, emulsification ability and co-surfactant efficiency assessment oil: Clove oil (CO), surfactant Kolliphore CS 20 as well as co-surfactant PEG 400 was nominated to develop L-SMEDDS of ITZ.[16]

Construction of phase diagrams

Solubility assessments, emulsification capability, and co-surfactant efficiency investigations were conducted to identify optimal formulations for the development of liquid-SMEDDS of ITZ. Ternary phase diagrams were utilized to compare and select the most promising system among the options presented in Table 1, with the evaluation criterion being the extent of the emulsification area generated by every system.

Pseudo-ternary phase diagrams were fabricated for every scheme utilizing the water titration way at room temperature to determine the optimal component concentrations for SMEDDS. Surfactant mixtures were formulated at three diverse mass proportions (1:1, 2:1, as well as 3:1). Numerous oil-to-S_{mix} weight ratios were mixed and heated, then titrated with water while observing visual transitions. Endpoint compositions were used to calculate phase percentages and generate phase diagrams utilizing PCP disso V3 software. Six diagrams were created to compare microemulsion regions for different S_{mix} ratios in every system.[17]

Preparation of Liquid SMEDDS of Itraconazole

Subsequent the analysis of the ternary phase diagram, considering the impact of drug loading and the pH of the dissolution medium, system-1 comprising clove oil (CO) as the oil phase, Kolliphor 20 (KCS 20), and PEG 40 was chosen for formulating L-SMEDDS of Itraconazole. Nine different trial formulations of ITZ L-SMEDDS were prepared based on the composition of system-1, maintaining a constant Itraconazole concentration of 100 mg in every formulation. The concentration ranges for the components were as follows: 400 to 600 mg for clove oil (CO), 300 to 500 mg for surfactant (Kolliphor 20, KCS 20), and 150 to 250 mg for co-surfactant (PEG 400). The ratio (Km=2, 2:1 w/w) remained consistent throughout the formulations. This specific proportion of oil to surfactant mixture was calculated based on the demonstrated microemulsion-producing capability of these mixtures observed in the phase diagram study.

In the preparation process, ITZ was introduced into a glass vial containing the appropriate quantity of clove oil (as the oily phase). The blend was heated in a water bath at 40 to 50°C and cyclomixed. Then, surfactants as well as co-surfactants were added and heated again. After cyclomixing for 10 minutes, an isotropic system with ITZ solubilization was obtained. The products were transferred to glass vials for evaluation at room temperature.[17]

Optimization of ITZ L-SMEDDS

SMEDDS, being thermodynamically stable systems, are made at specific concentrations of oil, surfactant, and co-surfactant without phase parting or other issues. Designated preparations underwent numerous thermodynamic stability tests, including freeze-thaw cycles and centrifugation. Surviving formulations were then assessed for dispersibility and %transmittance.

Freeze-thaw cycles and centrifugation

To assess thermodynamic stability, formulations underwent three freeze-thaw cycles involving freezing at -4°C for 24 hours and monitored through softening at 40°C for 24 hours. Visual inspection for phase separation and drug precipitation was conducted subsequently during every cycle. Subsequent the cycles, L-SMEDDS underwent centrifugation at 3000 rpm

Table 1: Composition of two different combination systems employed to construct a ternary phase diagram

System No.	*Oil*	*Surfactant*	*Co-surfactant*
System-1	Clove oil (CO)	Kolliphore CS 20	PEG 400
System-2	Anise oil (AO)	Gelucire 48/16	Trascutol HP

for 5 minutes. Preparations presenting not any signs of drug were chosen for subsequent studies.

Robustness to dilution

L-SMEDDS formulations of ITZ were subjected to numerous levels of dilution in different mediums with different pH values to simulate gradual dilution encountered *in-vivo*. Every formulation was diluted to 100 and 1000-fold in three distinct dissolution mediums (SGF, SIF, and SAB). The diluted microemulsions were kept at room temperature for 12 hours and visually inspected for %transmittance (%T), appearance (AP), as well as drug precipitation (DP). The preparation demonstrating resilience to dilution was deemed optimized.[17,18]

Estimation of Optimized Preparations of ITZ L-SMEDDS

Globule size, PDI and ZP analysis

About 50 mg of the optimized ITZ L-SMEDDS was mixed with 50 mL of SGF, SIF, and SAB. The Horiba Zetasizer (SZ-100 nanoparticle series instrument) was accustomed to measuring the resultant microemulsion's mean globule size, polydispersity index (PDI), and zeta potential (ZP).[18]

Morphology of globules by transmission electron microscopy

Transmission electron microscopy (TEM) investigation was directed on microemulsions derived from diluting optimized ITZ L-SMEDDS (ILS1) in distilled water. Samples were diluted 1000-fold, stained with 2% phosphotungstic acid for 30 seconds, and positioned on copper grids for surveillance. Imaging and examination were performed utilizing Tecnai Imaging and Analysis software.[18]

Drug content analysis

Precisely measure the optimized ITZ L-SMEDDS (ILS6), equivalent to 100 mg of ITZ, and place it in a 50 mL volumetric flask. Fill the flask with methanol and sonicate it in a bath sonicater for 15 to 20 minutes to extract the ITZ. Filter the methanolic extract utilizing Whatman filter paper, and then dilute the extract with the mobile phase. The reverse-phase high-performance liquid chromatography (RP-HPLC) method was employed to analyze the drug content, in addition to the sum of ITZ was assessed utilizing the calibration curve equation.[18]

In-vitro dissolution examination for L-SMEDDS

The study of dissolution of plain ITZ powder as well as optimized L-SMEDDS of ITZ (ILS6), corresponding towards 100 mg of ITZ, was examined utilizing USP apparatus-I at 37 ± 2°C and 100 rpm. Three dissolution mediums (SGF, SIF, and SAB) were used to assess the effect of pH on drug release. About 5 mL aliquots were removed at set intermissions, repositioned per fresh buffer, filtered, and diluted with dissolution medium. ITZ release was quantified utilizing HPLC.[19]

Preparation and Characterization of Solidified SMEDDS

Selected as the solidifying agent (solid carrier), Sylloid 244 FP (S2F) was employed to develop powdered-SMEDDS of ITZ. The binding capacity of S2F for the L-SMEDDS of ITZ was specifically investigated utilizing the methodology outlined. The conversion of the L-SMEDDS into a free-flowing powder, namely P-SMEDDS of ITZ, was monitored the same procedure detailed. Subsequently, the obtained P-SMEDDS of ITZ was carefully filled into glass vials as well as deposited at room temperature for supplementary evaluations.[20,21]

Differential scanning calorimetric

Thermal examination was directed utilizing a Shimadzu DSC-50 to assess thermo-tropic properties. Samples weighing 3 to 5 mg were heated in aluminum pans at 10ºC/min underneath N_2 stream (20 mL/min), from 0 to 230ºC. Pure ITZ, a 1:1 w/w mixture of Sylloid 244 FP, and the P-SMEDDS formulation were analyzed.[22]

Powder X-ray diffraction pattern

The physical state of ITZ in powder SMEDDS was assessed *via* powder X-ray diffraction (PXRD) measurements utilizing a Bruker D2 Phase X-ray diffractometer. Measurements were conducted at room temperature with Cu-Kα radiation, spanning a 2Θ series of 10 to 50°C at 5°/min perusing speed. Samples of pure ITZ powder, Sylloid 244 FP, a physical blend of ITZ and Sylloid 244 FP (1:1 w/w), and ITZ P-SMEDDS were analyzed.[21]

Morphological analysis of P-SMEDDS by scanning electron microscopy

The external macroscopic structure of plain ITZ powder, Sylloid 244 FP, and ITZ P-SMEDDS was analyzed utilizing scanning electron microscopy (SEM) with Quanta 200 and Nova Nano SEM 600, operating at 10 kV. Specimens were attached onto SEM stubs with double-sided adhesive tape, coated with gold ions, and imaged at various magnification levels to assess surface morphology of ITZ crystals, Sylloid 244 FP, and ITZ P-SMEDDS.[21]

Result of solidification on globule size, PDI and zeta potential

A 100 mg portion of P-SMEDDS was dissolved in 100 mL of distilled water utilizing a magnetic stirrer at 500 rpm for 15 to 20 minutes. The dispersion was then left to stand for 2 hours to allow the adsorbing agent to settle. The supernatant microemulsion was then centrifuged at 8000 rpm for 10 minutes. The supernatant obtained after centrifugation was analyzed to determine the globule size, PDI, and ZP utilizing the Horiba Zetasizer (SZ 100).[21]

Formulation of Effervescent Granules of Itraconazole Powder SMEDDS

Selection of effervescent material and optimization of its concentration

The wet granulation method was used to prepare the effervescent granules of powder SMEDDS of ITZ. In total, three different formulations were tried, in every formulation, the amount

Table 2: Composition of ITZ effervescent SMEDDS

S. No	Material	Quantity (per unit)			
		E-SMEDDS 1 (1:1 w/w) (mg)	*E-SMEDDS 2 (1:0.75 w/w) (mg)*	*E-SMEDDS 3 (1:0.5 w/w) (mg)*	*E-SMEDDS 4 (1:0.25 w/w) (mg)*
1	ITZ P-SMEDDS	1950	1950	1950	1950
2	Sodium bicarbonate	730	560	365	183
3	Citric acid	1200	900	600	300
4	Aspartame	10	10	10	10
5	Magnesium stearate	75	70	35	17
Total E-SMEDDS per unit (mg/pouch) equivalent to 100 mg of ITZ		3965	3490	2960	2460

of P-SMEDDS was kept constant (1950 mg equivalent to 100 mg of ITZ). The quantity of effervescent material (Sodium bicarbonate and citric acid) was different from the P-SMEDDS to Effervescent material ratio of 1:1, 1:075, 1:0.5 and 1:0.25 w/w ratio. The quantity of every ingredient used is shown in Table 2. According to geometrical dilution, all ingredients of the formulation were mixed thoroughly to maintain good distribution of the P-SMEDDS with effervescent ingredients, and then powder mass was passed through sieve no 20. These obtained effervescent powders were dried at 40ºC overnight in a hot air oven.[22]

Evaluation of E-SMEDDS

Effervescence time

The effervescent time of ITZ E-SMEDDS was measured by adding one dose of E-SMEDDS powder to a glass encompassing 250 mL of H_2O when a clear solution is obtained, the effervescent time will be recorded. The arithmetic mean of triplicate readings was recorded.

Micromeritic properties

The produced E-SMEDDS should be filled in pouch for dispensing; hence, it should agree with good flowability. The flow property of selected E-SMEDDS (E-SMEDDS 3) was evaluated through computing the Angle of repose, bulk density (BD), tapped density (TD), Carr's Index (CI) and Hausner ratio.

Angle of repose

The angle of repose for the chosen E-SMEDDS of ITZ was calculated utilizing the stationary height funnel technique. It was calculated utilizing the subsequent formula,

$$\text{Angle of repose } (\theta) = \tan^{-1} (2h/d) \text{ ------ (1)}$$

Where,

θ = Angle of repose (º),

h = Height of the pile (mM),

d = Average diameter (n = 3) of the powder cone (mM)

Bulk density

The bulk density (BD) of the E-SMEDDS was measured by carefully pouring 10 g of the E-SMEDDS through a glass funnel into a 50 mL graduated measuring cylinder. The volume employed through the E-SMEDDS was noted, and the BD was calculated accordingly.

$$\text{BD (g/mL)} = \text{Weight of E-SMEDDS (g)/Volume occupied by E-SMEDDS (mL) ----- (2)}$$

Tapped density

The tapped density (TD) of the E-SMEDDS was measured by placing 10g of the E-SMEDDS into a 50 mL graduated measuring cylinder through a funnel. The cylinder was tapped from a height of 2 inches, awaiting a consistent volume was achieved. The volume engaged through the E-SMEDDS afterward pattern was noted, and the TD was calculated utilizing the provided formula.

$$\text{TD (g/mL)} = \text{Weight of E-SMEDDS (g)/volume occupied by E-SMEDDS (mL) ----- (3)}$$

Carr's index (%Compressibility)

The compressibility of the E-SMEDDS was assessed utilizing the subsequent formula:

$$\% \text{ Compressibility} = (TD\text{-}BD/TD) \times 100 \text{ ------- (4)}$$

Hausner ratio

The Hausner ratio, which is an indirect indicator of powder flowability, was calculated using the subsequent formula.

$$\text{Hausner ratio} = TD/BD \text{ -------- (5)}$$

Drug content

About 100 mg of ITZ E-SMEDDS was softened in methanol in a 50 mL volumetric flask. The mixture was manually shaken and then sonicated for 10 to 15 minutes. After settling for 15 minutes, the supernatant was sifted over and done with Whatman filter paper. The filtrate was diluted with methanol, and the drug content was analyzed utilizing RP-HPLC, determining the ITZ amount through the calibration curve equation.[22]

In-vitro dissolution study

The dissolution study of ITZ E-SMEDDS and a marketed capsule formulation (100 mg) was investigated utilizing USP apparatus II at 37 ± 0.5°C with a rotation speed of 50 rpm in three dissolution mediums: 0.05 M Sodium acetate buffer pH 4.5, SGF, and SIF. About 5 mL aliquots were withdrawn at intervals, repositioned through fresh buffer, filtered through Whatman filter paper, and diluted with the dissolution medium. ITZ release was quantified utilizing the HPLC method.[20-22]

In-vivo study

Pharmacokinetic examination of ITZ was directed in healthy wistar rats fasted for 12 hours and with feeding of normal food for 12 hours before administering the test product. Itraconazole plain API & marketed product (Sporonox Capsules 100 mg) were used as a reference product. Itraconazole effervescent granules were evaluated as a test product with a target label claim of 100 mg as well as half concentration of 50 mg. All products except itraconazole effervescent granules with half concentration of 50 mg were evaluated in fasted & fed conditions in cross-over study. Half concentration test product (50 mg) was evaluated only in fasted condition.

The body weight of the wistar rats ranged from 0.25 to 0.3 kg. Animals of group A & B were administered with dispersion of Itraconazole API in both fasted & fed conditions. Similarly, the marketed product (Sporonox Capsules) was administered to group C & D in fasted & fed conditions, respectively. Group E, F & G were administered with test product S-SMEDDS in fasted, fed condition at 100 mg label claim & in fasted condition at 50 mg label claim. Blood samples (approx. 0.5 mL) were withdrawn utilizing 2-2-2-2-2 replicate sparse sampling design. Blood sample was withdrawn from the tail vein and the concentration of itraconazole was checked after 0, 0, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12, and 24 hours. Specimens of blood collected at every time point were centrifuged at 5,000 rpm for 10 minutes using a high-speed centrifuge, in addition, plasma specimens were extracted then stored at -18°C awaiting supplementary investigation. Approval for this animal study was obtained from the ethical committee.

RESULTS

Solubility Study of ITZ in Numerous Vehicles (Buffer Medium and Oily Phases)

Figure 1 illustrates the solubility of ITZ in water and numerous buffer solutions. The findings indicate that ITZ solubility is pH-dependent. ITZ exhibits poor aqueous solubility, with solubility in water measured at just 0.024 ± 0.003 mg/mL. Among the buffers tested, ITZ solubility was highest in 0.1N HCl (0.124 ± 0.047 mg/mL), monitored through sodium acetate buffer at pH 4.5 (0.081 ± 0.012 mg/mL). Weak bases like itraconazole (pKa = 3.7) tend to have higher solubility at acidic pH levels because of their conversion to an uncharged state. However, their solubility decreases at neutral pH values. Basic drugs with poor solubility may dissolve completely in the stomach owing to the abrupt pH upsurge or significant dilution of excipients and then precipitate in the intestine. It is important to prevent precipitation and sustain their dissolved state in a neutral medium to enhance the absorption of such basic drugs. This examination aimed to develop ITZ-loaded SMEDDS to enhance solubility and augment *ex-vivo* intestinal penetration by providing ITZ in the form of molecular nanocarriers.

Oil selection is critical in formulating SMEDDS to prevent drug precipitation in the gut. The oil phase plays a key part in solubilizing the hydrophobic/lipophilic active ingredient, enhancing drug loading and bioavailability. The choice of oil

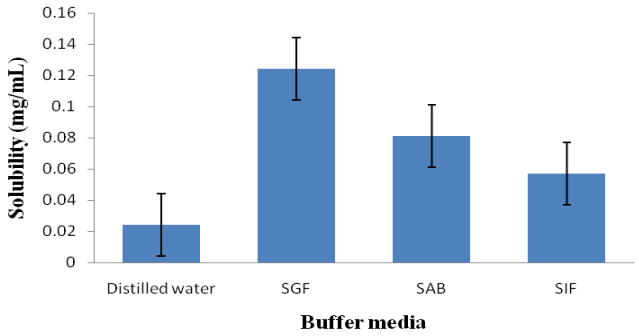

Figure 1: Solubility profile of ITZ in numerous buffer medium

significantly impacts the preparation's capability to dissolve the drug effectively in the body. Optimal drug loading relies on selecting oil with the highest solubilization capacity for the specific medicine being studied. The solubility profile of ITZ in oils was examined to choose the finest oils from a variation of different natural and synthetic oil phases. The failure of natural and synthetic oils to solubilize ITZ is explained by the findings of the approximate solubility research and primary screening of oils (Table 3).

Six oils, namely sesame pure oil, olive oil, anise oil, clove oil, isopropyl myristate, capmul MCM C8 NF, as well as capmul PG 8 NF (ITZ solubility more than 100 mg/g of oil), were chosen from the above screening for the quantitative measurement of ITZ solubility. According to the literature, itraconazole is more soluble in acidic environments.

Figure 2 depicts the findings of the estimated solubility of ITZ in nominated oils. Solubility of ITZ in sesame pure oil, olive oil, isopropyl myristate, capmul MCM C8 NF and capmul PG 8 NF was found to be 67.21 ± 1.09, 61.12 ± 1.19, 87.56 ± 3.45, 84.54 ± 3.78 and 78.45 ± 2.01 mg/g, respectively. Amongst all oils used, the solubility of itraconazole was found to be high in anise oil (235.18 ± 8.56 mg/gm) and clove oil (220.58 ± 5.45 mg/gm).

Emulsification Efficiency Study

In selecting surfactants and co-surfactants for optimized SMEDDS formulations, emphasis should be placed on their ability to spontaneously emulsify chosen oils rather than just solubilize the active ingredient. In the subsequent study, all available surfactants and co-surfactants were tested for their emulsification efficiency with designated oil: Anise oil and clove oil.

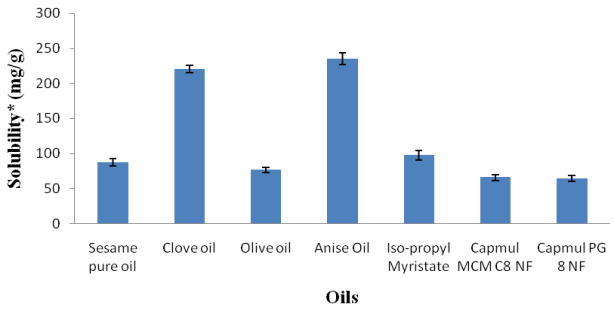

Figure 2: Quantitatively estimated of solubility of ITZ in numerous oils

Table 3: Approximate solubility of ITZ in numerous oily phase

S. No.	*Oil*	*No. of unit dose (50 mg) added*	*Visual observation*	*Approximate solubility (mg/g)*
1.	Arachis oil	1	Insoluble	<50
2.	Coconut oil	1	Slightly soluble	<50
3.	Sesame pure oil	2	Sparingly soluble	<100
4.	Linseed oil	1	Slightly soluble	<50
5.	Tea tree oil	1	Slightly soluble	<50
6.	Clove oil	5	Sparingly soluble	<250
7.	Olive oil	2	Sparingly soluble	<100
8.	Anise oil	5	Soluble	<250
9.	Sunflower oil	1	Slightly soluble	<50
10.	Soyabean oil	1	Insoluble	<50
11.	Shark liver oil	1	Slightly soluble	<50
12.	Isopropyl myristate	2	Sparingly soluble	<100
13.	Ethyl oleate	1	Sparingly soluble	<50
14.	Oleic acid	1	Insoluble	<50
15.	Maisine CC	1	Slightly soluble	<50
16.	Captex 200	1	Slightly soluble	<50
17.	Captex 500	1	Slightly soluble	<50
18.	Captex 300 EP NF	1	Sparingly soluble	<50
19.	Capmul MCM C8 NF	2	Sparingly soluble	<100
20.	Capmul PG 8 NF	2	Sparingly soluble	<100

Selection of Surfactant

The flask inversion technique was employed to evaluate numerous surfactants' capacity to emulsify specific oil phases—clove oil (CO). and anise oil (AO) individually. Efficiency was determined based on the amount of flask inversions (FI) needed to achieve an even emulsion and the resulting emulsion's transmittance values (%T).

Transmittance values and appearance of emulsion produced by different surfactants with CO are demonstrated in Table 4, it was observed that CO gets emulsified easily with a maximum number of surfactants employed, except caprol PEG 860, gelucire 50/13, span 80, span 20 and lauro glycol 90. These surfactants showed an inability to emulsify CO and produce turbid emulsion with less than 60%T. On the other hand, except these five surfactants, all other surfactants tried, produced either whitish or colloidal emulsion with more than 75% T. Emulsion produced by utilizing Tween 80, Cr-RH40, Cr-EL, PoL-188, PoL-407, labrasol and labrafac CC showed more than 75%T but less than 90%T. Among the surfactants, Kolliphor CS 12 and Kolliphor CS 20 (KCS-20) produced a fine clear and transparent microemulsion with 93.95 and 97.26% T, respectively and both required less than 10 flask inversions (FI).

Kolliphor CS 20 was found to be the best surfactant to emulsify clove oil and produced fine transparent microemulsion.

Transmittance values and appearance of emulsion produced by different surfactants with AO are demonstrated in Table 4, it was observed that, as compared to CO, AO did not emulsify easily with many surfactants employed and produced emulsion with more than 70% T. Surfactants like Tween 80, labrasol and labrafac CC were incapable of emulsifying AO, but they could potentially emulsify CO and produce whitish emulsion. Amongst all surfactants, cremophor RH40, gelucire 48/16, Kolliphor P407 and Kolliphor CS12 found capable of emulsifying AO and produces microemulsion with more than 85 %T. Gelucire 48/16 was found to be the best surfactant to emulsify AO and produced transparent microemulsion (91.59%T) but required more than 30 flask inversions.

On the basis of its emulsification ability and bioactive role, Kolliphore CS 20 was selected as surfactant for CO & oil system and finalized as clove oil for supplementary studies.

Selection of Co-surfactant

Incorporating a co-surfactant in surfactant-encompassing formulations reduces interfacial tension, fluidizes the hydrocarbon section of the interfacial film, and enhances drug absorption. Co-surfactants improve the spontaneity of self-emulsification efficiency and enhance the micro-emulsification of certain surfactants.

Amongst 10 different co-surfactants employed, n-butanol and plurol oleique 497 showed inability as a co-surfactant, produce whitish/colloidal emulsion on the other hand ethanol, propylene glycol, transcutol HP, PEG 400, labrafil M2125 cs and labrafil M 1944 cs found to be better co-surfactant to emulsify clove oil along with surfactant Kolliphor CS 20. All these co-surfactants produce microemulsion with more than 85%T. PEG 400 produces fine and clear microemulsion with more than 99%T and requires only 3 flask inversion to achieve this (Table 5).

Table 4: Emulsification Efficiency of surfactants for clove oil

S. No.	*Surfactant*	*No. of FI*	*%T*	*Appearance*
1	Cremophor EL	10	83.26	Whitish
2	Cremophor RH 40	8	86.59	Whitish
3	Caprol PGE 860	43	46.89	Turbid
4	Gelucire 48/16	42	57.45	Colloidal
5	Tween 20	10	68.10	Bluish white
6	Tween 80	8	79.26	Clear and Transparent
7	Span 20	20	53.56	Colloidal
8	Span 80	23	57.55	Colloidal
9	Lauroglycol 90	41	52.88	Turbid
10	Kolliphor CS 12	8	93.95	Clear and Transparent
11	Kolliphor CS 20	8	97.26	Clear and Transparent
12	Poloxamer L-407	35	78.56	Whitish
13	Poloxamer L-188	35	77.51	Whitish
14	Labrasol	18	83.78	Whitish
15	Labrafac CC	17	82.13	Whitish

*Values are expressed as mean (n = 2)

Pseudo Ternary Phase Diagram of CO: KCS 20: PEG 400 (System-1)

Two distinct systems were chosen from the aforementioned studies to formulate the SMEDDS of ITZ. Pseudo-ternary phase diagrams were developed towards augment the formulation components for L-SMEDDS of ITZ. These systems create fine oil-water emulsions upon moderate agitation in an aqueous medium. Surfactant and co-surfactant adsorb at the interface, decreasing interfacial energy and enhancing thermodynamic stability. Therefore, oil and surfactant selection and their mixing ratios (oil to S/CoS and surfactant to co-surfactant) are critical for microemulsion formation.

The diagram of System-1; Oil: Clove oil (CO), surfactant: Kolliphore CS 20 (KCS 20) and co-surfactant: PEG 400 was constructed by changing the surfactant: Co-surfactant ratios (Km), study performed utilizing three different Km values as shown in Figure 3.

In the ternary plots of system-1, the apexes represent 100% w/w concentration of individual excipients, with the blue quotas indicating the microemulsion region. At Km = 2, System-1 exhibited a broader microemulsion region compared to Km = 1 and Km = 3. The microemulsion area expanded with increasing surfactant (KCS 20) concentration up to a 2:1 proportion with co-surfactant. However, the microemulsion region began to decrease beyond a 2:1 ratio (Km = 3). Additionally, increasing the surfactant ratio resulted in reduced flowability. Therefore, system-1 was found suitable for emulsifying high concentrations of the oily phase (Clove oil) upon aqueous dilution, specifically with a 2:1 w/w ratio of surfactant (Kolliphor CS 20) to co-surfactant (PEG 400). Diverse proportions of surfactant to co-surfactant decreased the efficiency of emulsifying the oily phase upon aqueous dilution. Based on these findings, Km = 2 (a proportion of 2:1) was selected for further evaluation of the effects of drug loading and pH of dilution medium on system-1.

Formulation of Liquid SMEDDS (ITZ L-SMEDDS)

In total nine diverse trial formulation bunches of ITZ L-SMEDDS were prepared utilizing the composition of

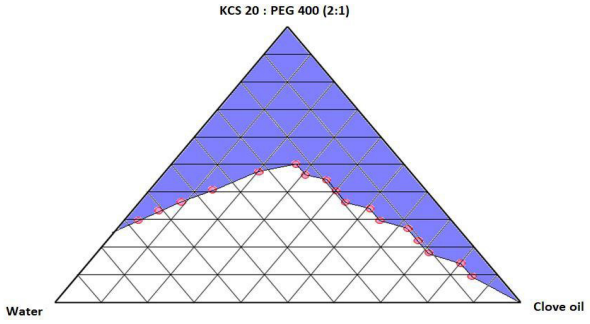

Figure 3: Pseudo ternary phase diagram consisting of oil phase (CO), S- Cos (KCS 20: PEG 400) and water utilizing K_m=2

Table 5: Extemporaneity of emulsification through co-surfactants for surfactant Kolliphor CS 20 (KCS 20)

S. No.	*Co-surfactant*	*Oil: Clove oil (CO) surfactant: Kolliphor CS 20 (KCS 20)*		*Appearance*
		No. FI	*%Transmittance*	
1	Lauroglycol FCC	12	83.24	Whitish
2	Ethanol	10	88.45	Slight bluish
3	N-Butanol	10	78.47	Whitish
4	Isopropyl alcohol	12	83.21	Whitish
5	Propylene glycol	8	87.11	Slight bluish
6	Transcutol HP	6	89.23	Slight bluish
7	PEG 400	3	99.87	Clear and transparent
8	Plurol oleique 497	22	72.87	Colloidal
9	Labrafil M 2125 Cs	8	85.23	Bluish whitish
10	Labrafil M 1944 Cs	8	87.23	Bluish whitish

*Values are expressed as mean of two individual observations

Table 6: Composition of ITZ Liquid SMEDDS (IL-SMEDDS)

	ITZ L-SMEDDS formulation code								
Components (mg)	*ILS_1*	*ILS_2*	*ILS_3*	*ILS_4*	*ILS_5*	*ILS_6*	*ILS_7*	*ILS_8*	*ILS_9*
ITZ	100	100	100	100	100	100	100	100	100
Clove oil	400	400	400	500	500	500	600	600	600
Kolliphor CS 20	300	400	500	300	400	500	300	400	500
PEG 400	150	200	250	150	200	250	150	200	250
O : S_{mix}	1:1.125	1:1.5	1:1.875	1:0.9	1:1.2	1:1.5	1:0.75	1:1	1:1.25

systems-1 as outlined in Table 6. Oil: CO surfactant: Kolliphor 20 (KCS 20) and Co-surfactant: PEG 400. The amount of itraconazole (100 mg) was retained in every preparation. The concentration of CO used in the range of 400 to 600 mg, surfactant: kolliphor 20 (KCS 20) was used in the range of 300 to 500 mg and co-surfactant PEG 400 was used in the range of 150 to 250 mg. The proportion of Surfactant: Co-surfactant (Km = 2, 2:1 w/w) was kept constant in every preparation.

Optimization of ITZ L-SMEDDS

Chosen formulations underwent numerous thermodynamic stability tests, including a freeze-thaw cycle and centrifugation. Preparations that approved these stability tests were then assessed for dispersibility and %transmittance. The observations of the freeze-thaw cycle and centrifugation study of formulation produced from the system-1 is provided in Table 7. It was observed that, ILS_1, ILS_2, and ILS_3 showed instability on the very first freeze-thaw cycle and these batches didn't show several indications of phase parting (oil and S_{mix}) but suffered from drug separation. This may be because of a low level of oily phase (Clove oil). So, the ILS_1, ILS_2, and ILS3 batches were discarded and further cycles of evaluation of these batches was not performed (NP).

Batches from ILS_4 to ILS_9 were subjected to further evaluation cycles. It was observed that except ILS_4, all other batches passed a further 2 cycles monitored by centrifugation, and no indication of phase parting or drug precipitation was observed. The reason of such observation is the volume of the oily phases, which can efficiently solubilize the target dose of ITZ. Batch ILS_4 showed crystals of drug precipitation on centrifugation and there was separation of oil and surfactant phase too. This could be because of the lower concentration of surfactant mixture and oily phase. Based on the result of this study, batch no ILS5 to ILS9 were subjected to robustness in the dilution study.

Robustness to Dilution Study

Table 8 illustrates the impact of dilution volume and pH of the dilution medium on ITZ-comprising SMEDDS (ILS5–ILS9). Physical integrity and drug solubilization capacity of the post-dilution microemulsion were assessed. All formulations were extemporaneously distributed and made microemulsions through <10 FI, showing no drug precipitation. Formulations ILS5, ILS6, and ILS9 remained clear or slightly bluish, with transmittance values exceeding 95% even after 12 hours, regardless of the pH of the dilution medium. Conversely, formulations with a surfactant mixture of moderate concentration were observed. ILS_7 and ILS_8 were capable of producing microemulsion spontaneously, but the microemulsion was not so clear, and it was bluish-white in appearance, with less than 93%T. Formulations ILS_5, ILS_6, and ILS9 had equal potential to produce microemulsions

Table 7: Optimization of ITZ L-SMEDDS (System-1) formulation

Test and parameter	*ITZ L-SMEDDS formulation code*								
	ILS_1	*ILS_2*	*ILS_3*	*ILS_4*	*ILS_5*	*ILS_6*	*ILS_7*	*ILS_8*	*ILS_9*
	Freeze thaw cycle								
	1^{st} cycle								
Phase separation	Stable								
Drug precipitation	Un-stable	Un-stable	Un-stable				Stable		
	2^{nd} cycle								
	NP	NP	NP				Stable		
	NP	NP	NP				Stable		
	3^{rd} cycle								
	NP	NP	NP				Stable		
	NP	NP	NP				Stable		
	Centrifugation study								
	NP	NP	NP	Un-stable			Stable		
	NP	NP	NP	Un-stable			Stable		

Table 8: Optimization of ITZ L-SMEDDS (System-1) formulation

Code	*Dilution medium*	*Dilution*	*Evaluation parameters*		
			% Transmittance	*Appearance*	*Drug precipitation*
ILS_5	0.1N HCl (SGF)	100	96.21	Slightly bluish	Stable
		1000	95.37	Slightly bluish	Stable
	Phosphate buffer pH 6.8 (SIF)	100	96.61	Slightly bluish	Stable
		1000	95.15	Slightly bluish	Stable
	Sodium acetate buffer pH4.5 (SAB)	100	96.24	Slightly bluish	Stable
		1000	96.72	Slightly bluish	Stable
ILS_6	0.1N HCl (SGF)	100	97.53	Clear & transparent	Stable
		1000	99.29	Clear & transparent	Stable
	Phosphate buffer pH 6.8 (SIF)	100	97.39	Clear & transparent	Stable
		1000	98.12	Clear & transparent	Stable
	Sodium acetate buffer pH4.5 (SAB)	100	98.51	Clear & transparent	Stable
		1000	98.54	Clear & transparent	Stable
ILS_7	0.1N HCl (SGF)	100	87.21	Whitish	Stable
		1000	88.56	Whitish	Stable
	Phosphate buffer pH 6.8 (SIF)	100	88.24	Whitish	Stable
		1000	90.31	Whitish	Stable
	Sodium acetate buffer pH4.5 (SAB)	100	88.28	Whitish	Stable
		1000	89.72	Whitish	Stable
ILS_8	0.1N HCl (SGF)	100	90.46	Slightly bluish	Stable
		1000	91.16	Slightly bluish	Stable
	Phosphate buffer pH 6.8 (SIF)	100	90.23	Slightly bluish	Stable
		1000	91.82	Slightly bluish	Stable
	Sodium acetate buffer pH4.5 (SAB)	100	90.42	Slightly bluish	Stable
		1000	92.51	Slightly bluish	Stable
ILS_9	0.1N HCl (SGF)	100	95.61	Clear & transparent	Stable
		1000	96.20	Clear & transparent	Stable
	Phosphate buffer pH 6.8 (SIF)	100	95.62	Clear & transparent	Stable
		1000	97.20	Clear & transparent	Stable
	Sodium acetate buffer pH4.5 (SAB)	100	96.48	Clear & transparent	Stable
		1000	96.91	Clear & transparent	Stable

*Values are articulated as mean (n = 2)

with globule sizes in the expected range of 50 to 200 nm. The microemulsion produced by these formulations were found to be clear and transparent with %Transmittance more than 95%. Amongst these formulations, ILS_5, ILS_6 were selected for further study. These formulations produced stable microemulsions same as that of the ILS_9; however, the total mass containing the target dose of ITZ was less than ILS_9 formulation.

Assessment of Optimized Preparation of ITZ L-SMEDDS

Globule size, PDI and ZP

Figures 4 and 5 display the fallouts of globule size as well as surface charge analysis for ITZ L-SMEDDS formulations. Table 9 indicates that the mean globule size for ILS5 ranged from 210 to 280 nm, while ILS6 ranged from 130 to 165 nm. The mean globule size of microemulsions from both optimized formulations was slightly larger in SIF compared to the other medium, although not significantly so. The PDI for both formulations across numerous mediums ranged from 0.45 to 0.75, indicating a smaller mean size as well as a tapered globule size scattering in the resulting microemulsions. The ZP of globules present in microemulsion produced from ILS_5 was found in the series of -16 to -21 mV, while ILS_6 produces globules with ZP in the series of -45 to -57 mV. The structure of the excipients employed includes fatty acids, which is why the surface charge of the droplet is typically negative. As a result, the outcomes for size, PDI, and ZP for itraconazole were found to be acceptable. Results suggested that these formulations will produce microemulsion in biological fluid that will not show coalescence and hence will be stable upon oral administration

Table 9: Data of the globule size, PDI and ZP ITZ L-SMEDDS (ILS_5 and ILS_6)

	Dilution medium								
	0.1N HCl (SGF)			*Phosphate buffer pH 6.8 (SIF)*			*Sodium acetate buffer pH 4.5 (SAB)*		
	Globule size (nm)[#]	*PDI* [*]	*ZP*[*] *(mV)*	*Globule size (nm)*[#]	*PDI* [*]	*ZP*[*] *(mV)*	*Globule size (nm)*[#]	*PDI* [*]	*ZP*[*] *(mV)*
ILS_5	210 ± 23.56	0.57	- 17.51	280 ± 27.56	0.51	- 16.41	234 ± 18.87	0.75	- 21.14
ILS_6	133 ± 14.12	0.73	- 51.23	165 ± 13.30	0.63	- 48.56	145 ± 13.30	0.47	- 57.12

#Globule size is conveyed as mean ± SD (n = 2)
*PDI and ZP are communicated as mean (n = 2)

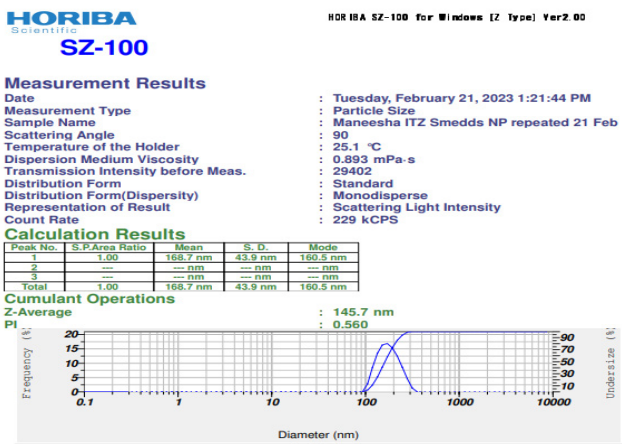

Figure 4: Globule size of optimised ITZ L-SMEDDS (ILS_6)

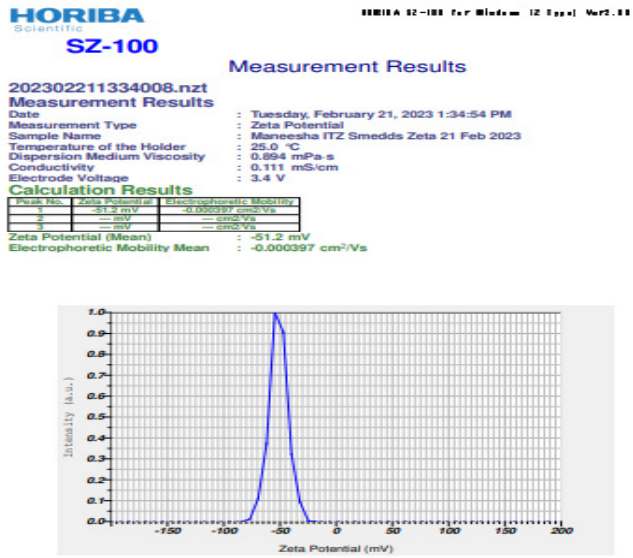

Figure 5: Zeta potential of optimised ITZ L-SMEDDS (ILS_6)

until they get absorbed. Based on the findings of globule size and ZP study, it was decided to select ILS_6 as an optimized formulation and evaluate further.

Transmission electron microscopy

Transmission electron microscopy (TEM) was conducted on the optimized L-SMEDDS formulation after dilution by distilled water at a 1000-fold ratio. The image (Figure 6) validates the capability of ITZ L-SMEDDS towards generating spherical oil

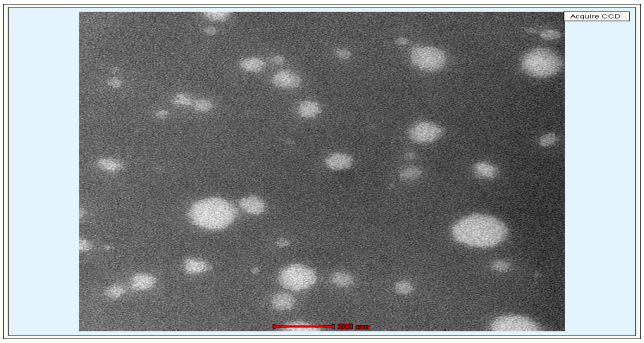

Figure 6: TEM image ITZ L-SMEDDS (ILS_6) in distilled water

globules of nano size, consistently circulated across the film. This observation from the TEM image reaffirms the findings from the globule size examination.

Drug content

The drug content of ILS6 was observed in the acceptable series of 99.35 ± 2.36%. Findings suggested that ITZ is evenly distributed in the developed L-SMEDDS.

In-vitro Dissolution

Figures 7(a) and (b) depict the *in-vitro* dissolution profiling of pure ITZ aqueous solution as well as optimized ITZ L-SMEDDS (ILS6) across various dissolution media. Pure ITZ showed pH-dependent release, with maximum release in 0.1N HCl pH 1.2. Conversely, ILS6 exhibited over 95% drug release within 30 minutes in all tested media. The improvement in the dissolution profile of ILS6 is significant, indicating potential enhancement in the oral bioavailability of ITZ, a poorly soluble class-II drug. The preparation's ability to enhance dissolution suggests improved drug release as well as absorption, particularly in conditions mimicking the GIT.

Preparation and Characterization of Solidified SMEDDS

Based on the findings of earlier literature reports, Sylloid 244 FP (S2F) was evaluated for its adsorbing capacity to adsorb L-SMEDDS of ITZ. It was observed that S2F was able to adsorb greater L-SMEDDS of ITZ. S2F could adsorb around 2300 mg of ITZ L-SMEDDS per 1-gm and still maintain good flow properties. The composition of developed P-SMEDDS of ITZ is shown in Table 10.

DSC: Thermal analysis

Figure 8 presents DSC thermograms of plain ITZ, a physical blend of ITZ and Syloid 244 FP (1:1 w/w), and the P-SMEDDS. Plain ITZ demonstrated a sharp endothermic peak at 170.02°C,

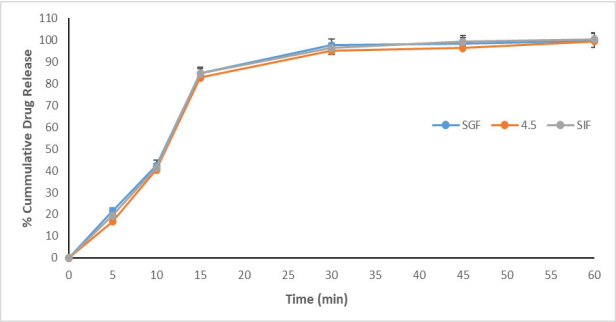

Figure 7(a): *In-vitro* dissolution profiling of ITZ L-SMEDDS (ILS_6) in numerous dissolution medium

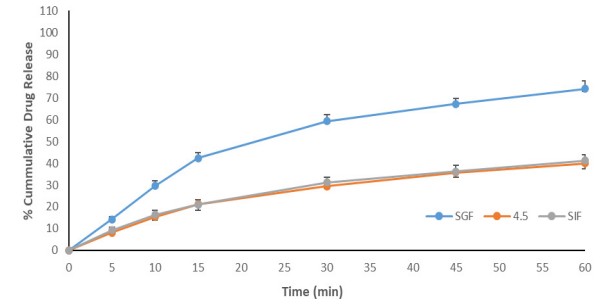

Figure 7(b): *In-vitro* dissolution profiling of plain ITZ in numerous dissolution medium

indicating its crystalline nature. Syloid 244 FP showed no peaks. The physical mixture displayed a lesser strong peak at 167.87°C owing to crystalline ITZ. Notably, the nonexistence of discernible ITZ peaks in the P-SMEDDS suggests altered melting behavior and prevention of crystallization, possibly due to solubilization by lipid surfactants as well as physical mingling through a solid carrier.

Powder X-ray diffraction pattern

Figure 9 shows XRD graph of plain ITZ, neat Syloid 244 FP, a physical mixture of ITZ and Syloid 244 FP, and ITZ P-SMEDDS. Plain ITZ exhibited sharp peaks, indicating crystallinity. Neat Syloid 244 FP showed no intrinsic peaks. The physical mixture displayed reduced intensity of ITZ peaks, suggesting a dilution effect with Syloid. In ITZ P-SMEDDS, intense ITZ peaks were absent, indicating a transformation to an amorphous state within the lipid matrix. This transformation is consistent with DSC results, suggesting compatibility between ITZ and Syloid 244FP.

Table 10: Composition of ITZ powder SMEDDS

Components	*Quantity (mg) per unit formula*
ITZ	100
Clove oil	500
Kolliphor CS 20	500
PEG 400	250
L-SMEDDS	1350
Sylloid 244 FP	600
Total powder SMEDDS	1950

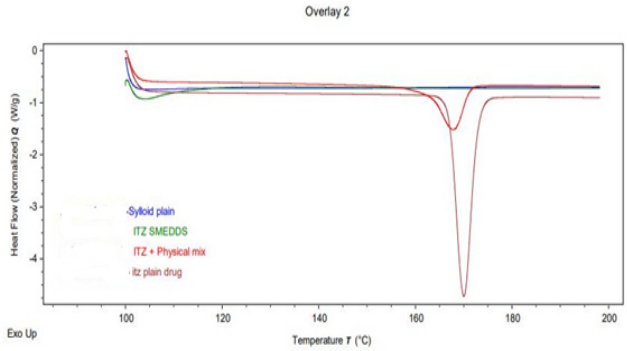

Figure 8: Overlay DSC thermogram of plain ITZ, plain Syloid 244 FP, physical mixture of ITZ and syloid 244 FP and ITZ powder SMEDDS

Morphology of P-SMEDDS by scanning electron microscopy

The scanning electron microscopy (SEM) image in Figure 10(a) displays ITZ as rectangular crystalline structures measuring approximately 60 to 75 µm. Figure 10(b) illustrates syloid 244 FP as spherical porous particles with a size ranging from 1 to 3 µm. In Figure 10(c), micrographs of P-SMEDDS reveal liquid SMEDDS absorbed onto the surface of sylloid particles. Partially covered sylloid particles are also visible because of the process of physical mixing that facilitates adsorption. Characteristic crystalline structures of ITZ are absent in P-SMEDDS micrographs, suggesting the drug exists in a completely dissolved state within the solid SMEDDS.

The outcome of solidification on globule size characteristics of ITZ SMEDDS preparation

Solidification of the ITZ SMEDDS formulation onto syloid 244 FP through physical mixing was assessed. The mean globule size of L-SMEDDS (ILS6) was 133 ± 14.12 nm, although the mean droplet size of powder SMEDDS was 182.2 ± 7.12 nm. The increase in globule size in P-SMEDDS was attributed to the bimodal distribution observed due to the occurrence of

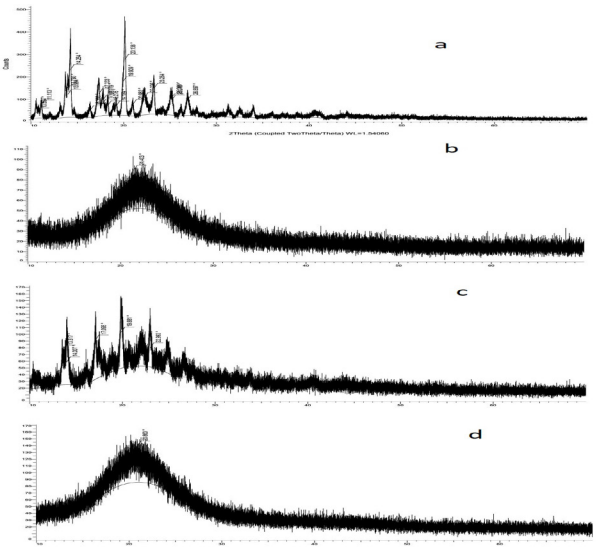

Figure 9: XRD graph of plain ITZ (a) plain Syloid 244 FP (b) physical mixture of ITZ (c) Syloid 244 FP and (d) ITZ P-SMEDDS

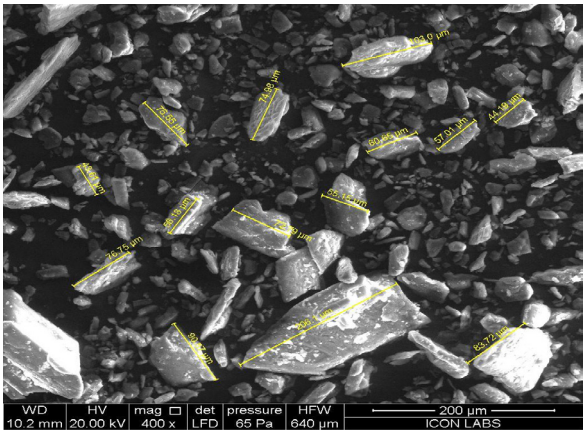

Figure 10(a): SEM images of plain ITZ

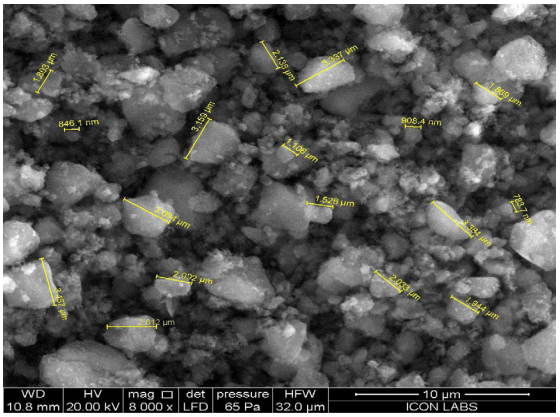

Figure 10(b): SEM images of plain Syloid 244 FP

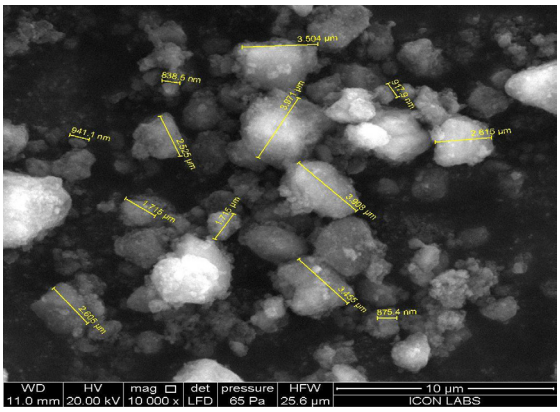

Figure 10(c): SEM images of ITZ P-SMEDDS

syloid 244 FP particles. In the solid SMEDDS samples, the larger syloid 244 FP particles were allowed to sediment, and then the microemulsion sample was tested for droplet size, resulting in a bimodal distribution. Globule size and PI of ITZ P-SMEDDS in SGF is presented in Figure 11a. Zeta potential f-ITZ P-SMEDDS in SGF is presented in Figure 11b

Development and Evaluation of ITZ E-SMEDDS

When formulating solid-SMEDDS of ITZ, the key goal was to leverage its self-emulsifying properties to generate fine

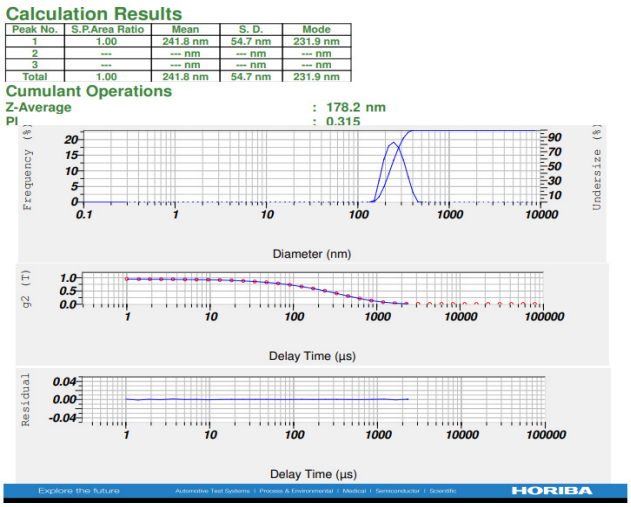

Figure 11(a): Globule size and PI of ITZ P-SMEDDS in SGF

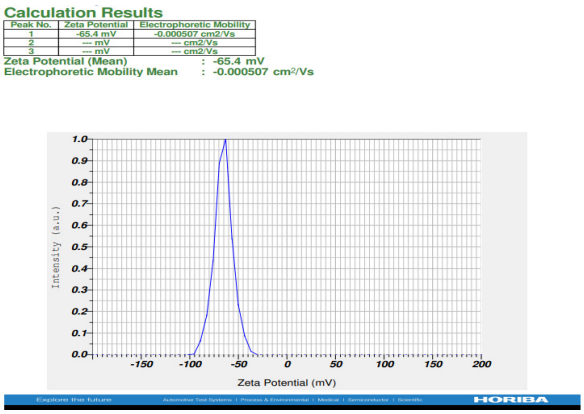

Figure 11(b): Zeta potential f-ITZ P-SMEDDS in SGF

microemulsions with small globule sizes, thereby augmenting the dissolution and bioavailability of the poorly soluble ITZ. Additionally, the aim was to capitalize on the benefits of S-SMEDDS, which comprise enhanced patient compliance as well as formulation stability. The composition of the ITZ effervescent SMEDDS (E-SMEDDS) is outlined in Table 11.

Evaluation of ITZ E-SMEDDS

Effervescence time

It was observed that less than 30 seconds is required for complete dispersion of P-SMEDDS in water for formulations that contain 1:1, 1:0.75 and 1:0.5 w/w ratio of P-SMEDDS: Effervescent material (Table 12). Formulation containing P-SMEDDS: Effervescent material in the proportion of 1:0.25 w/w failed in the direction of providing complete dispersion even after 2 minutes. This indicated that the lowest concentration of Effervescent material required to produce complete dispersion of P-SMEDDS in water was about 1:0.5 w/w proportion of P-SMEDDS and Effervescent material.

Micromeritic properties

The flow properties of E-SMEDDS produced after adding effervescent material to ITZ P-SMEDDS were evaluated.

Table 11: Formula composition of ITZ effervescent SMEDDS

S. No	*Material*	*Quantity (per unit)*			
		E-SMEDDS 1 (1:1 w/w) (mg)	*E-SMEDDS 2 (1:0.75 w/w) (mg)*	*E-SMEDDS 3 (1:0.5 w/w) (mg)*	*E-SMEDDS 4 (1:0.25 w/w) (mg)*
1	ITZ P-SMEDDS	1950	1950	1950	1950
2	Sodium bicarbonate	730	560	365	183
3	Citric acid	1200	900	600	300
4	Aspartame	10	10	10	10
5	Magnesium stearate	75	70	35	17
Total E-SMEDDS per unit (mg/pouch) equivalent to 100 mg of ITZ		3965	3490	2960	2460

Table 12: Effervescence time

S. No	*Material*	*Quantity (per unit)*			
		E-SMEDDS 1 (1:1 w/w)	*E-SMEDDS 2 (1:0.75 w/w)*	*E-SMEDDS 3 (1:0.5 w/w)*	*E-SMEDDS 4 (1:0.25 w/w)*
Effervescent time* (Sec)		10	25	30	2 minutes (incomplete)

* Values expressed as the mean (n = 3)

Flow properties were assessed through analysis of the angle of repose, TD, BD, %Compressibility, and Hausner ratio. Table 13 depicts the findings of this experiment. The angle of repose of ITZ E-SMEDDS was found to be "Good" as it was observed as 27º 83' ± 2º. An analogous statement was seen in Carr's index, which was found to be "Good" (14.07 ± 0.98) and Hausner ratio below 1.18. It was confirmed that E-SMEDDS of ITZ are produced by adsorbing L-SMEDDS on syloid 244 FP monitored by addition of effervescent material having good flow properties, which are required to even fill the formulations in sachet.

Drug content

Drug content of ITZ E-SMEDDS was found to be 102.73 ± 2.86%, the result indicates the uniformity in the distribution of ITZ-loaded P-SMEDDS in effervescent material.

In-vitro dissolution profile of ITZ E-SMEDDS

The drug dissolution from E-SMEDDS was analogous in the direction of L-SMEDDS, suggesting that the self-emulsifying properties of L-SMEDDS remained unchanged after conversion into powder and then effervescent SMEDDS, as illustrated in Figure 12. Self-emulsifying effervescence formulation of ITZ was found to be very fast dissolving & release was found to be pH independent.

In-vivo study

An oral bioequivalence study was conducted in healthy wistar rats fasted for 12 hours & also in fed conditions in a cross-over study design, as shown in Table 14. The effervescent granules for the formulation of S-SMEDDS of itraconazole were evaluated against plain API & marketed product in fasted & fed condition. Plasma concentration-time profiles are depicted in Figure 13. C_{max} and T_{max} were identified by examining individual drug plasma concentration-time curves. Pharmacokinetic parameters such as AUC and T1/2 for all

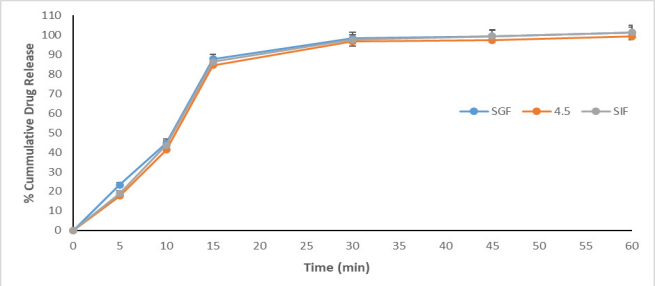

Figure 12: *In-vitro* dissolution profile of ITZ E-SMEDDS in numerous dissolution medium

Table 13: Flow properties of ITZ E-SMEDDS

Parameter	*E-SMEDDS 3 (1:0.5 w/w)*
Angle of repose	27º 83' ± 2º
BD *(g/mL)	0.3623 ± 0.019
TD*(g/mL)	0.4131 ± 0.026
Compressibility *(%)	14.07 ± 0.98
Hausner ratio*	1.18

* Values are expressed as mean ± SD (n = 3), BD-bulk density, TD-Tapped Density

formulations are listed in Table 14. A substantial upsurge in C_{max} & AUC was observed in the effervescent granules formulation of SMEDDS as compared to both marketed capsules & plain API. An increase in these parameters indicates increased in solubility & bioavailability for SMEDDS formulation.

DISCUSSION

The study aimed to enhance the solubility and dissolution rate of ITZ by utilizing an effervescence system with E-SMEDDS.[23] It involved formulating L-SMEDDS and solidifying the

Table 14: Pharmacokinetic parameters

Formulation details		*Itra API-Fasted*	*Itra API-Fed*	*Sporonox-Fasted*	*Sporonox-Fed*	*Itra S-SEDDS (100 mg)-Fasted*	*Itra S-SEDDS (100 mg)-Fed*	*Itra S-SMEDHS (50 mg)-Fasted*
Comparative	Units	Group A	Group B	Group C	Group D	Group E	Group F	Group G
$t_{1/2}$	h	1.26 ± 0.22	1.98 ± 0.28	2.20 ± 0.31	1.07 ± 0.28	2.28 ± 0.32	1.60 ± 0.22	1.74 ± 0.22
T_{max}	h	4 ± 0.12	4 ± 0.14	4 ± 0.18	4 ± 0.13	4 ± 0.19	4 ± 0.14	4 ± 0.11
C_{max}	µg/mL	6.20 ± 0.34	5.44 ± 0.35	10.08 ± 0.22	9.68 ± 0.22	17.32 ± 0.42	17.19 ± 0.35	13.20 ± 0.23
AUC_{0-t}	µg/mL*h	18.53 ± 0.42	16.50 ± 0.27	35.56 ± 0.32	26.26 ± 0.30	55.12 ± 0.12	52.69 ± 0.43	32.12 ± 0.22
AUC 0-inf_obs	µg/mL*h	23.77 ± 0.34	24.62 ± 0.22	45.38 ± 0.32	31.20 ± 0.28	66.69 ± 0.22	60.36 ± 0.28	43.20 ± 0.34

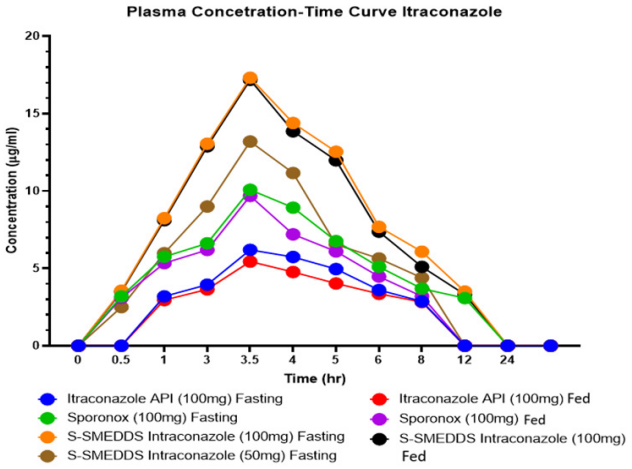

Figure 13: Pharmacokinetic parameters

optimal formulation (ILS6) into a solidified P-SMEDDS through adsorption on syloid (SYL). L-SMEDDS formulations were successfully developed with ILS6 exhibiting desirable characteristics such as nanosized droplets and stability.[24-26] The incorporation of S-SMEDDS into an effervescence system resulted in a promising formulation with improved solubility and dissolution profile for ITZ. The investigations highlighted the potential of combining self-micro-emulsifying systems and effervescent granules to augment the delivery of poorly water-soluble drugs.

CONCLUSION

In this study, nine L-SMEDDS formulations for ITZ were evaluated. The optimal formulation (ILS_6) was identified, comprising 40% clove as the oil, 40% Kolliphor CS 20 as the surfactant, and 20% PEG 400 as the co-surfactant. ILS_6 exhibited a droplet size of 130 to 165 nm, well below 200 nm, with a PDI value of 0.47 to 0.73, representing the development of an emulsion with nanosized droplets and even distribution. The formulation demonstrated stability across numerous tested conditions and achieved maximum drug loading capacity. The solidification of the optimized L-SMEDDS into S-SMEDDS utilizing sylloid 244 FP yielded a free-flowing powder without drug interactions. The incorporation of S-SMEDDS into effervescent granules was achieved utilizing diverse excipients. The selected effervescence system of granules successfully passed quality control and stability tests. The effervescent granules have very fast release profile, which is pH-independent. The synergistic effect of the SMEDDS and effervescence system collectively contributed in the direction of the enhanced solubility and dissolution of itraconazole.

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