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Design, Optimization and Characterization of Itraconazole Loaded Self-Nanoemulsifying System for the Ophthalmic delivery

Projeto, Otimização e Caracterização de um Sistema Auto-Nanoemulsionável Carregado com Itraconazol para Administração Oftálmica

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ABSTRACT

The triazole medication is an active medicinal ingredient that is highly effective against the dermatophyte, Candida, and Aspergillus species. Being a BCS II medication, responsible for most of its poor bioavailability in ocular region. The present study focuses on the development of a self-nanoemulsifying drug delivery system (SNEDDS) designed to improve the solubility and ophthalmic bioavailability of itraconazole. Screening of appropriate oils, surfactants, and co-surfactants was carried out through solubility profiling. A water dilution method was applied to evaluate emulsification capacity. The formulation was optimized using a 3^2 factorial design. The optimized batch demonstrated a droplet size of 60.6 nm, PDI of 0.46, and zeta potential of -11.2 mV. Drug content was found to be 93.25%. In vitro drug release followed anomalous transport with an 'n' value ≥0.85, indicating release pattern was controlled by a combined interaction of diffusion and polymer swelling mechanisms. An antifungal assay revealed significantly enhanced inhibition of *Candida albicans* growth by the optimized SNEDDS. In comparison to its marketed eye drop (ITRAL 1% w/v), an improved property of Itraconazole loaded self-nanoemulsifying system was noticed, and *in vitro* data suggest it is an alternative to eye drop. Assessment of different parameters -: such as minimal droplet size, optimal surfactant concentration, desired viscosity, excellent in vitro drug release, shorter self-emulsification time, and appropriate drug content -: revealed that the optimized batch was the most suitable formulation for further in vivo and ex vivo studies to establish its potential as an effective and efficient ophthalmic delivery system.

Keywords Itraconazole, Ocular delivery, Self-Nanoemulsifying system, SNEDDS.

RESUMO

O medicamento triazol é um ingrediente medicinal ativo altamente eficaz contra as espécies dermatófitos, Candida e Aspergillus. Sendo um medicamento BCS II, responsável pela maior parte da sua fraca biodisponibilidade na região ocular. O presente estudo concentra-se no desenvolvimento de um sistema auto-nanoemulsificante de administração de medicamentos (SNEDDS) projetado para melhorar a solubilidade e a biodisponibilidade oftálmica do itraconazol. A triagem de óleos, surfactantes e co-surfactantes apropriados foi realizada através do perfil de solubilidade. Um método de diluição em água foi aplicado para avaliar a capacidade de emulsificação. A formulação foi otimizada utilizando um planejamento fatorial 3^2. O lote

otimizado demonstrou tamanho de gota de 60,6 nm, PDI de 0,46 e potencial zeta de -11,2 mV. O conteúdo da droga foi de 93,25%. A liberação in vitro do medicamento seguiu transporte anômalo com um valor 'n' ≥0,85, indicando que o padrão de liberação foi controlado por uma interação combinada de mecanismos de difusão e inchaço do polímero. Um ensaio antifúngico revelou inibição significativamente aumentada do crescimento de Candida albicans pelo SNEDDS otimizado. Em comparação com o colírio comercializado (ITRAL 1% p/v), foi observada uma propriedade melhorada do sistema autonanoemulsificante carregado com Itraconazol, e dados in vitro sugerem que é uma alternativa ao colírio. A avaliação de diferentes parâmetros - como tamanho mínimo de gotícula, concentração ideal de surfactante, viscosidade desejada, excelente liberação in vitro do medicamento, menor tempo de autoemulsificação e conteúdo adequado do medicamento -: revelou que o lote otimizado foi a formulação mais adequada para estudos adicionais in vivo e ex vivo para estabelecer seu potencial como um sistema de administração oftálmica eficaz e eficiente.

Palavras-chave: Itraconazol, entrega ocular, sistema auto-nanoemulsificante, SNEDDS.

INTRODUCTION

Due to the significant prevalence of fungi infections and the slow advancement of new antifungal compounds, the pharmaceutical industry was compelled to suggest innovative drug delivery systems that could be applied topically or taken orally. Improved antifungal bioavailability with reduced toxicity is a key requirement for such delivery systems. [1,2]

ophthalmic antifungal preparations are typically delivered as eye drops in the form of solutions or suspensions.[3] Due to corneal impermeability and a short residence time in the ocular mucosa, they are often poorly absorbed.[4] The brief retention period of eye drops is mainly due to the limited volume of the precorneal area. The lacrimal reservoir in the conjunctiva-sac can accommodate only about 7–10 µL of tear fluid, whereas the total precorneal capacity reaches approximately 30 µL. A typical eye drop volume (~50 µL) exceeds this capacity, resulting in the loss of nearly 40% of the administered dose.[5] Therefore, repeated eye drop treatments are necessary to solve this issue and achieve the minimal therapeutic efficacy. Unfortunately, repeated instillations result in nasolacrimal absorption, which compromises patient compliance and has systemic side effects.[6]

Despite poorly water-soluble drug eye drops can easily penetrate the lipophilic cornea, their therapeutic efficacy is frequently constrained by low aqueous solubility and poor ocular bioavailability. Accordingly, various strategies have been explored to enhance drug solubility and ocular retention, thereby improving ocular absorption.[7]

The triazole medication class includes the well-known antifungal medicine Itraconazole (ITZ). It is an active medicinal ingredient that is highly effective against the dermatophyte, Candida, and Aspergillus species. Deep fungal infections like histoplasmosis and aspergillosis respond well to ITZ treatment. Dermatomycosis and other superficial fungal diseases can be effectively treated with it.[8] Due to its poor solubility and inadequate absorption, ITR in capsule dosage form has an absolute bioavailability of just 55% when taken with food. Being a BCS II medication, it's extremely low aqueous solubility (1 ng/mL) is responsible for most of its poor bioavailability.[9] The incorporation of such therapeutic molecules into inert lipid carriers in the nano-metric range may accelerate drug solubility and increase bioavailability. Therefore, Self-nanoemulsifying systems (SNESs) may potentially provide a significant improvement in the in vitro performance of medications that are poorly water-soluble and hence may be effective delivery systems for ocular therapies.

SNES offers a uniform, clear, and stable liquid formulation. Being a thermodynamically stable anhydrous formulation, it self-assembles into a fine nanoemulsion when gently mixed with aqueous fluids. By generating low interfacial tension and a large interfacial area, SNES enhances solubilization and facilitates efficient encapsulation of poorly water-soluble drugs within oil droplets, resulting in improved drug permeation. Appropriate excipient selection—encompassing oil, surfactant, and co-surfactant, depends on the drug's solubility profile, the emulsification capa-

city, the self-emulsification zone, and the resulting particle size characteristics.[10, 11]

Considering these factors, this research work aimed to develop, optimize, characterize, and evaluate itraconazole (ITZ)-loaded self-nanoemulsifying systems (SNES) to enhance drug solubility for the effectively treats ocular fungal infections. Solubility evaluation of ITZ in multiple oils, surfactants, and co-surfactants was performed, and the emulsification performance was assessed using aqueous dilution testing. Formulation optimization was performed using a factorial design approach, followed by evaluation of globule size, polydispersity index, viscosity, self-emulsification time, *In-vitro* precipitation characteristics, and *In-vitro* drug release.

MATERIALS AND METHODS

Itraconazole (ITZ) generously supplied by Allkind Healthcare Unit-III, Himachal Pradesh, India. Isopropyl myristate and propylene glycol were procured from LOBA Chem Pvt. Ltd., Mumbai, India, while soya oil was purchased from Rajesh Chemicals, Mumbai, India. S D Chemicals, Mumbai, India supplied olive oil, Tween 80, oleic acid, span 20, and PEG 200. PEG 400 and castor oil were acquired from Mohini Organics Pvt. Ltd., Mumbai, India. Methanol, meeting HPLC grade standards, was procured from LOBA Chem. All remaining reagents and chemicals employed in the study were of analytical reagent grade and met the requisite purity standards.

Saturation solubility of Itraconazole in various oils, surfactants and co-surfactants Different oils evaluated to establish specific emulsification zones, and the solubility of itraconazole was evaluated in cottonseed oil, isopropyl myristate (IPM), isopropyl palmitate (IPP), castor oil, oleic acid, olive oil, soya oil, and cod liver oil. Surfactants (Tween 80, Span 80) and co-surfactants/co-solvents (propylene glycol, PEG 200, and PEG 400) were also assessed. A surplus quantity of itraconazole was introduced into 10 mL of each vehicle and subjected to orbital shaking for 48 h until equilibrium was reached.[12] The equilibrated samples were then centrifuged at 4000 rpm for 15 min; the clear supernatant was withdrawn, diluted appropriately with methanol, and quantified by spectrophotometry at 257 nm (λmax).

PREPARATION AND OBSERVATION OF SELF--EMULSIFYING REGION BY WATER DILUTION METHOD

Upon contact with aqueous media and gentle agitation, SNEDDS spontaneously produces a fine oil-in-water nanodispersion. The surfactant and co-surfactant/co-solvent reduce interfacial tension by adsorbing at the oil–water interface, thereby preventing globule coalescence and enhancing emulsion stability. Preliminary trial formulations were prepared using varying concentrations of oils (10–90% v/v), surfactants (45–5% v/v), and co-surfactants (45–5% v/v), selected based on solubility studies. In all formulations, the total composition was maintained at 100%. This design enabled evaluation of the influence of oil and surfactant levels on the emulsification process. Each trial batch was visually assessed for transparency, turbidity, or milkiness, and the exact compositions of oil, surfactant, and co-surfactant for each trial are presented in Table 1. The ternary mixtures were homogenized using magnetic stirring until a uniform system was obtained. Subsequently, The blend was thereafter introduced dropwise to a fixed volume of water under gentle stirring, and the resulting appearance was observed to assess emulsion formation.[13]

Table 1. Dilution compositions of ternary mixtures with water (1:1 S_{mix})

Sr. No.	Oleic acid + IPM (1:1) (%v/v)	Tween 80 (%v/v)	PEG 400 (%v/v)	Dilute with Distilled water
1	10	45	45	100
2	20	40	40	100
3	30	35	35	100
4	40	30	30	100
5	50	25	25	100
6	60	20	20	100
7	70	15	15	100
8	80	10	10	100
9	90	5	5	100

*IPM: Isopropyl myristate; PEG: Polyethylene glycol.

PREPARATION OF BATCHES OF ITRACONAZOLE LOADED SELF-NANO EMULSIFYING DRUG DELIVERY SYSTEM USING 3^2 FACTORIAL DESIGNS

SNEDDS batches containing itraconazole were prepared by dispersing the drug at 0.1% w/v (equivalent to 1 mg/mL) within oil–surfactant–cosurfactant blends, ensuring that the total component ratio for each mixture added up to 100%. Dissolution was achieved through constant stirring at 25°C using REMI Equipment Pvt. Ltd., Mumbai. Until a transparent mixture was obtained. Nine SNEDDS formulations were produced following a 3^2 full factorial scheme, and each batch was characterized with respect to visual clarity, droplet size, surface charge, and size distribution index.[14]

Table 2. Formulation formula for 3^2 factorial design

Factors: Formulation Variables	Levels (ml)		
Independent variables	-1	0	+1
Tween 80 (X1)	40	45	50
PEG 400 (X2)	44	45	46
Dependent variables	**Goals**		
Particle Size (nm)	Minimize		
Zeta Potential (mV)	Minimize		
Polydispersity index	Minimize		

*PEG: Polyethylene glycol.

EVALUATION OF ITRACONAZOLE LOADED SELF-NANO EMULSIFYING SYSTEM DETERMINATION OF GLOBULE SIZE, POLYDISPERSITY INDEX (PDI) AND ZETA POTENTIAL OF ITZ- LOADED SNES

Each ITZ-loaded SNEDDS (10 mg/system) was diluted 1:100 v/v with distilled water and continuously stirred magnetically for 1 min. prior to measurement. Hydrodynamic diameter and polydispersity index were measured by dynamic light scattering using a Zetasizer Nano ZS (Malvern Instruments, Malvern, UK) maintained at 25°C employing a He–Ne laser (632 nm).[15]

ASSESSMENT OF SELF-EMULSIFICATION TIME

The self-emulsifying capability of the formulated SNES was evaluated by determining the emulsification time. Briefly, A 1 mL aliquot of ITZ-loaded SNES (10 mg/mL) was introduced into 200 mL of pre-warmed simulated tear fluid (pH 7.4, 37 °C) under continuous magnetic agitation. The emulsification process was visually monitored, and the time required for complete self-emulsification was recorded.[16]

DRUG CONTENT (%)

To determine drug content, 1 mL of the SNEDDS (corresponding to 1 mg itraconazole) was dissolved in a solvent mixture comprising methanol (2 mL) and distilled water (8 mL) in a 10 mL volumetric flask. A 0.1 mL portion of this solution was subsequently diluted to a final volume of 10 mL using distilled water. The Absorbance was recorded at 262 nm on a double-beam UV–Visible spectrophotometer (Shimadzu, Japan); a blank formulation was used as the reference standard.[17]

DILUTION STUDY

To mimic in vivo dilution conditions, the impact of dilution on emulsion stability was evaluated. One milliliter of each formulation underwent dilution 10-, 100-, and 1000-fold with either distilled water or simulated tear fluid (pH 7.2), followed by magnetic stirring at 100 rpm and 37 °C to ensure uniform mixing. The After dilution, all samples were kept at ambient temperature for 24 h and examined visually for any evidence of phase instability.[18]

Formulation performance in vitro of the formulations was assessed utilizing a visual grading system. Grade A indicated rapid formation of a clear or bluish transparent emulsion within 1 min; Grade B represented quick emulsification with a slightly less clear, bluish-white appearance; Grade C denoted the formation of a milky fine emulsion within 2 min; Grade D corresponded to slow emulsification (>2 min) producing a dull, greyish-white and slightly oily emulsion; and Grade E signified inadequate emulsification, evidenced by visible oil droplets floating on the surface.

VISCOSITY

At 25± 0.5°C, diluted versions of the SNEDDS formulas were tested for viscosity with Brookfield viscometer equipped with 61 no. spindle and a shear rate of 100 rpm.

pH

All microemulsion samples had their pH levels determined at 25^0C± 0.5^0C using a pH metre (Digital systronic, Mumbai, India). Which was measured using standard buffer solutions pH 4, pH 7. Triplicate readings were taken for every parameter.[19]

IN-VITRO DIFFUSION STUDY

An *In vitro* drug release was assessed utilizing a Franz diffusion cell. The receptor compartment was filled with 13 mL of simulated tear fluid (STF, pH 7.4 ± 0.2), while 3 mL of itraconazole-loaded SNEDDS was placed in the donor compartment. A cellophane membrane pre-soaked in STF was mounted between the two compartments as the diffusion barrier. The entire assembly was thermostatically controlled at 37 ± 0.5 °C with constant magnetic agitation at 50 rpm. Samples of 1 mL each were collected at predetermined time intervals (0.5, 1, 2, 4, 6, and 10 h) in triplicate; each withdrawn volume was promptly replaced with an equivalent volume of fresh STF to preserve sink conditions. The samples were analyzed spectrophotometrically at 262 nm using a blank as reference, and drug release was quantified using a previously established calibration curve.[20]

DRUG RELEASE KINETICS MODELLING

Using release kinetics approach of drug release, the release kinetics of itraconazole from microemulsion were determined and modelled using the Higuchi model, first order release kinetics, and zero order release kinetics. Information about the releases was calculated using many factors. The Korsmeyer–Peppas equation was utilized to establish the release exponent (n), release rate constant (k), and regression coefficient (R).[21]

IN-VITRO ANTIFUNGAL ACTIVITY

For antimycotic assessment, 5 mL and 10 mL specimens were preserved under refrigerated conditions until use. Antifungal efficacy was assessed by the agar well diffusion technique with Sabouraud dextrose agar (SDA; HiMedia) as the growth medium. SDA was prepared by dissolving it in distilled water to obtain an acidic pH (5.5–5.6) with a high glucose content (40%), followed by sterilization by autoclaving at 121 °C for 15 min. Under aseptic conditions, 25 mL of molten SDA was dispensed into sterile Petri dishes (100 mm × 15 mm) and left to solidify at room temperature. Fungal spores were suspended in normal saline, adjusted to 1 mL, and quantified using a hemocytometer. Using a sterile borer, uniform wells of 6 mm diameter were cut into the solidified agar, and Into each well, 100 µL of the respective test solution (10 mg/mL) was carefully dispensed. The plates were placed in an incubator at 29 °C for 72 h, after which the diameters of the inhibition zones (mm) were measured as an index of antifungal activity.[23]

RESULTS SOLUBILITY DETERMINATION OF ITRACONAZOLE IN DIFFERENT OILS

Solubility investigations offer understanding into the drug-loading capacity of the formulation, as oils can solubilize lipophilic drugs only up to a certain extent. For formulating a topical SNEDDS intended for ocular application, the drug's solubility was assessed across a range of oils, surfactants, and co-surfactants. Based on these studies, voriconazole showed the highest solubility in a combination of oleic acid and isopropyl myristate (2.46 ± 0.05 mg/mL).

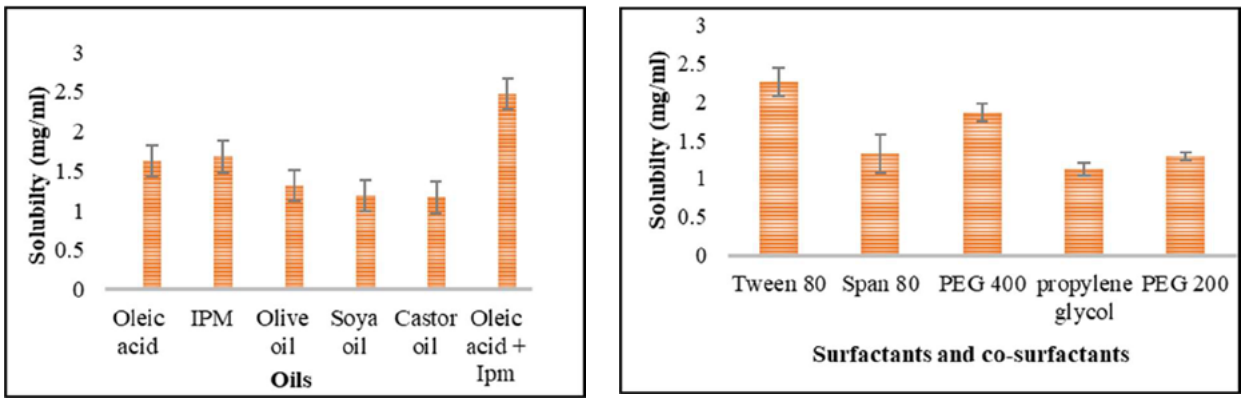
There are various components with surfactant qualities that can be used in microemulsion systems; however, the options are limited because very few surfactants are suitable for the eye. Non-ionic surfactants are typically preferred for ophthalmic use. Itraconazole demonstrated superior solubility in Tween 80 (2.26 ± 0.18 mg/ml) and in co-surfactant propylene glycol (1.85 ± 0.11 mg/ml) relative to the other excipients tested depicted in table and shown in figure. Tween 80 along with polyethylene glycol 400 exhibit HLB values of 15 and 20, respectively. For the formation of an oil-in-water nanoemulsion, a high-HLB surfactant is typically combined with a suitable co-surfactant to achieve optimal interfacial stabilization. As non-ionic surfactants and co-surfactants do not ionize in solution, Accordingly, Tween 80 and propylene glycol were identified as the most suitable surfactant and co-surfactant pair for this formulation.

Table 3. Solubility study using different oils

Sr. No.	*Oils*	*Solubility (mg/ml)*	Surfactants & Co-surfactants	*Solubility (mg/ml)*
1	Oleic acid	1.62±0.38	Tween 80	2.26 ± 0.18
2	Isopropyl myristate	1.68±0.23	Span 80	1.32 ± 0.25
3	Olive oil	1.31±0.24	PEG 400	1.85 ± 0.11
4	Soya oil	1.18±0.12	Propylene glycol	1.12 ± 0.08
5	Castor oil	1.16±0.12	PEG 200	1.29 ± 0.04
6	Oleic acid + Isopropyl myristate	2.46 ± 0.05		

*Values represented as mean ± SD (n=3)

Figure 1: Solubility studies of Itraconazole in different excipients.



PREPARATION AND OBSERVATION OF SELF-EMULSIFYING REGION BY WATER DILUTION METHOD

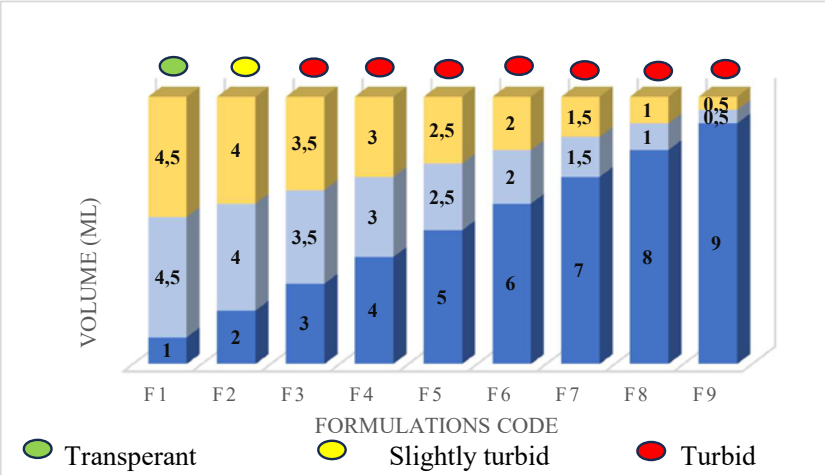
To find out optimum concentration of ternary mixture, preliminary trail batches were prepared using oil, surfactant, and cosurfactant (Ternary mixture) concentrations to study the effect of varying surfactant concentrations effect and characterise the Self-Nano Emulsifying region. Three-component mixtures underwent dilution with distilled water to evaluate their emulsification characteristics. For every initial formulation, the oil phase and a fixed Smix ratio (Tween 80:PEG 400, 1:1) underwent complete mixing in varying volume ratios ranging from 1:9 to 9:1. Nine oil–Smix combinations (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1) were prepared and diluted with water to assess transparency. Each formulation was carefully examined, and the oil–Smix ratio of 1:9 produced the highest transparency.

Table 4. Dilution study using different surfactants and co-surfactants

Sr. No.	Oleic acid + IPM (1:1) (mL)	Tween 80 (mL)	PEG 400 (mL)	Dilute with Fix amount of water (100 mL)
1	**1**	**4.5**	**4.5**	**Transparent**
2	2	4	4	Slightly Turbid
3	3	3.5	3.5	Turbid
4	4	3	3	Turbid
5	5	2.5	2.5	Turbid
6	6	2	2	Turbid
7	7	1.5	1.5	Turbid
8	8	1	1	Turbid
9	9	0.5	0.5	Turbid

*IPM: Isopropyl myristate, PEG: Polyethylene glycol.

Figure 2: Effect of formulation composition on dilution clarity of SNEDDS



OPTIMIZATION OF ITRACONAZOLE LOADED SELF-NANO EMULSIFYING DRUG DELIVERY SYSTEM USING 3^2 FACTORIAL DESIGN

A 3^2 full factorial design was implemented using Design-Expert® software (version 11.0, trial), yielding a total of nine experimental formulations. Tween 80 concentration (X_1) and PEG 400 concentration (X_2) served as the two independent factors, while particle size (Y_1), zeta potential (Y_2), and polydispersity index (Y_3) were chosen as response variables to evaluate the simultaneous effect of both factors on formulation characteristics.

DROPLET SIZE

Particle size of newly formulated ITZ-loaded SNEDDS formulations developed using factorial design was characterized. All formulations exhibited mean globule diameters under 100 nm, a desirable characteristic for ophthalmic use since the human eye tolerates particles of up to 10 µm. Upon dilution with water, the SNEDDS consistently formed nano-sized globules (<100 nm), confirming efficient self-nanoemulsification.[23] Particle size of newly formulated ITZ-loaded SNEDDS formulations (IS1–IS9) ranged from 90.6 to 41.2 nm, with IS1–IS5 exhibiting sizes between 90.6 and 60.6 nm and IS6–IS9 between 50.5 and 41.2 nm, as shown in the table. A decrease in droplet size was observed with increasing surfactant concentration, while a reduction in oil content further contributed to smaller globule sizes.

ZETA POTENTIAL

It indicates the surface charge and predicts the stability of nanodroplet systems. Generally, high positive or negative zeta potential values promote colloidal stability by generating electrostatic repulsion between similarly charged particles, thereby preventing aggregation.[24] Typically, nanoemulsion stability is generally attained when the zeta potential lies within the range of approximately −30 to +30 mV.[25]

Every formulation displayed negative zeta potential values ranging from −10.2 to −18.6 mV, as compiled in the table and illustrated in the corresponding figure. The observed negative surface charge on the SNEDDS likely arises from the non-ionic nature of the surfactant and co-surfactant.

POLYDISPERSITY INDEX

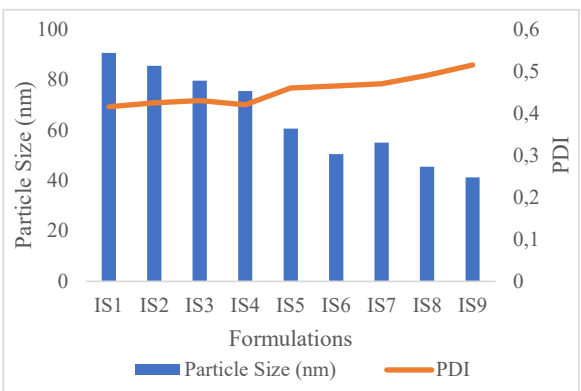
The polydispersity index (PDI) characterizes, breadth of the droplet size distribution and serves as an indicator of both formulation homogeneity and physical stability. PDI values between 0.01 and 0.5 represent a narrow size distribution, whereas values greater than 0.7 indicate a highly polydisperse system.[26] All formulations of displayed less than 0.7 PDI, which ranged from 0.416 to 0.515 as shown in the table and figure shows a graphical representation of all ITZ SNEDDS with a limited size distribution.

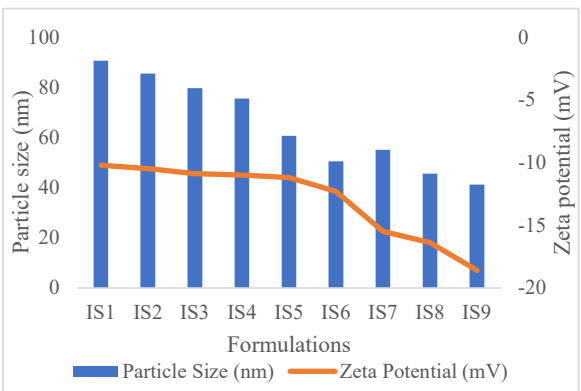
Table 5. Formulations Factors and their responses.

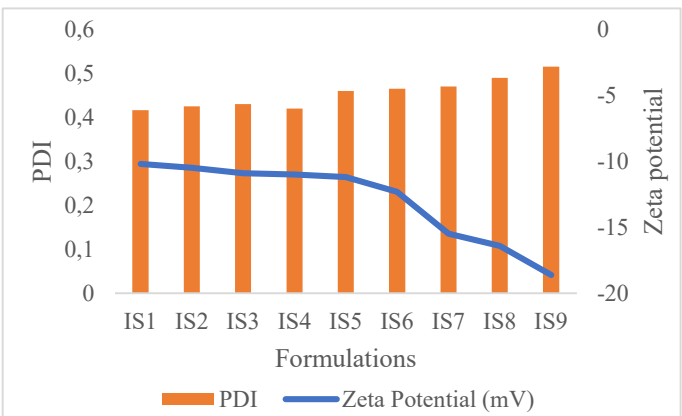
Formulation code	A: Conc. of Tween 80 (% v/v)	B: Conc. of PEG 400 (% v/v)	Particle Size (nm)	Zeta Potential (mV)	PDI
IS1	40	44	90.6	-10.2	0.416
IS2	45	44	85.5	-10.5	0.425
IS3	50	44	79.6	-10.9	0.43
IS4	40	45	75.5	-11	0.42
IS5	45	45	60.6	-11.2	0.46
IS6	50	45	50.5	-12.3	0.465
IS7	40	46	55	-15.5	0.47
IS8	45	46	45.5	-16.4	0.49
IS9	50	46	41.2	-18.6	0.515

*Conc.: Concentration, PDI: Polydispersity Index.

Figure 3: Summarized graphical presentation of Particle size, Zeta potential and PDI evaluations.







SELF-EMULSIFICATION TIME ASSESSMENT

Emulsification duration was established through visual observation the disappearance of the SNEDDS preconcentrate and the formation of a homogeneous nanoemulsion upon dilution.

Self-emulsification time serves as a key indicator of formulation efficiency, with an ideal SNEDDS exhibiting rapid and complete emulsification in an aqueous medium.[25] All formulations showed great self-emulsification in aqueous media.

DRUG CONTENT

ITZ-loaded SNEDDS drug content varied from 87.35 ± 1.2% to 89.63 ± 1.2%. The drug content of the various formulations is presented in the table and corresponding figure, with formulations IS5, IS6, and IS7 exhibiting drug content values above 90%.

VISCOSITY

Viscosity was determined, post-dilution at 25 ± 0.5°C using a Brookfield viscometer (CC3-14 spindle/100 rpm). Rheological assessment is essential for SNEDDS to physically characterize the system and ensure adequate stability upon dilution. SNEDDS viscosity has a crucial role in how well it disperses in water. Higher viscosities have a tendency to slow down the emulsification rate, which may have an impact on the bioavailability and *in vivo* drug release patterns.[26] All SNEDDS's showed optimum viscosities.

pH

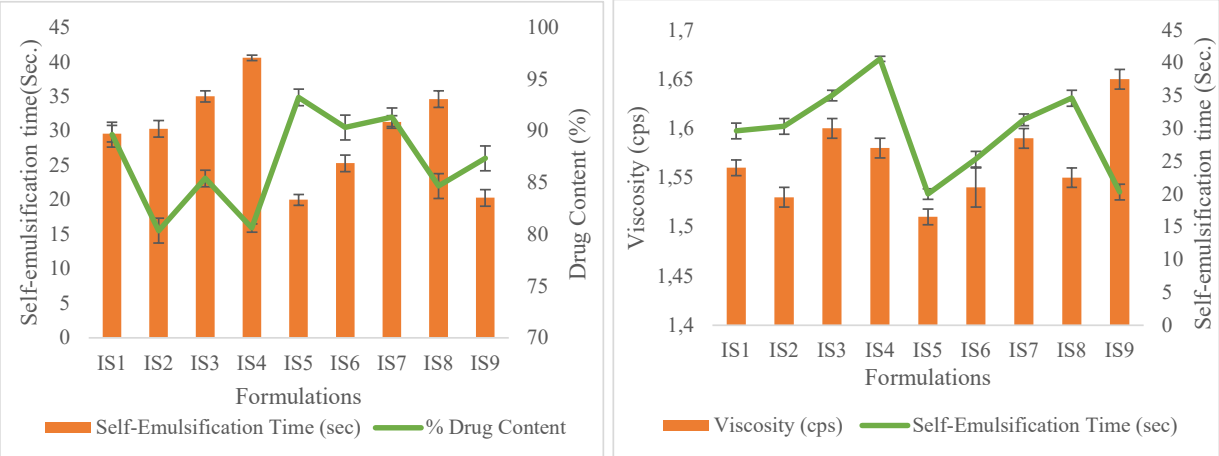
Following ophthalmic administration, the formulation stimulates tear secretion, and the tear fluid rapidly dilutes and buffers small quantities of added substances, enabling the eye to tolerate a wide pH range. For ophthalmic preparations, therapeutic agents should be isotonic and isohydric, with a pH range of 3.5–8.5 considered optimal to avoid corneal irritation or damage.[27] The pH values of the formulated SNEDDS ranged from 5.89 ± 0.11 to 6.39 ± 0.12, as presented in the table. These values fall within an acceptable ocular range, suggesting that the formulations are unlikely to significantly alter normal tear physiology following ocular instillation.

Table 6. Physical properties of Itraconazole Loaded Sel-Nanoemulsifying Systems.

Formulation Batch	Sel-emulsification Time (sec.)	% Drug content	Viscosity after dilution with distilled water (cps)	pH
IS1	29.6 ± 1.2	89.63 ± 1.2	1.56 ± 0.008	6.39 ±0.12
IS2	30.3 ± 1.2	80.36 ± 1.2	1.53 ± 0.01	6.16 ±0.14
IS3	35 ± 0.8	85.41 ± 0.8	1.60 ± 0.01	5.89 ±0.30
IS4	40.6 ± 0.4	80.62 ± 0.4	1.58 ± 0.01	6.52 ±0.13
IS5	20 ± 0.8	93.25 ± 0.8	1.51± 0.008	6.68 ±0.20
IS6	25.3 ± 1.2	90.32 ± 1.2	1.54 ± 0.02	6.29 ± 0.11
IS7	31.3 ± 0.9	91.33 ± 0.9	1.59 ± 0.01	6.57 ±0.08
IS8	34.6 ± 1.2	84.67 ± 1.2	1.55 ± 0.01	6.05 ±0.10
IS9	20.3 ± 1.2	87.35 ± 1.2	1.65 ± 0.01	5.89 ± 0.11

*Values represented as mean ± SD (n=3)

Figure 4: Summarization of various physical evaluation studies in graphical presentation.



DILUTION STUDY

For effective performance as an ophthalmic delivery vehicle, SNEDDS must remain physically stable during aqueous dilution, without exhibiting phase separation or drug crystallization. Upon aqueous dilution, the resulting nanoemulsions from most formulations appeared clear and optically transparent, with no detectable phase separation observed after 24 h. This characteristic demonstrates their appropriateness for ocular application, as stable emulsified oil globules are more likely to traverse the ocular surface without destabilization. Based on these observations, all ITZ-loaded SNEDDS formulations were stable upon dilution, except IS1, IS4, and IS7.

Figure 5: Thermodynamic stability assessment of itraconazole-loaded SNEDDS formulations (IS1–IS9) in distilled water (DW) and simulated tear fluid (STF) at different dilution volumes (10 mL and 100 mL).

Formulation	DW (10 mL)	DW (100 mL)	STF (10 mL)	STF (100 mL)
IS1	0	0	0	0
IS2	1	1	1	1
IS3	1	1	1	1
IS4	0	0	0	0
IS5	1	1	1	1
IS6	1	1	1	1
IS7	0	0	0	0
IS8	1	1	1	1
IS9	1	1	1	1

IN-VITRO DRUG RELEASE STUDY

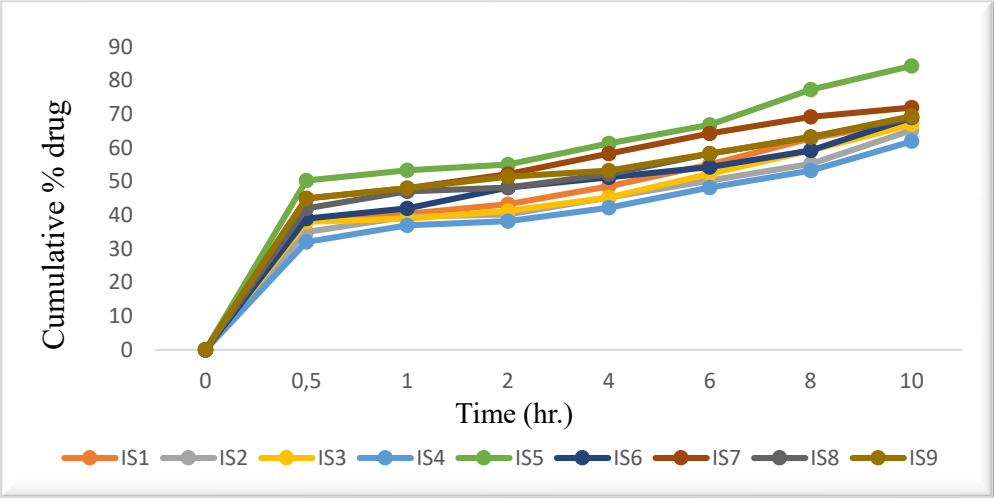
Cumulative *In-vitro* drug release data for ITZ-loaded SNEDDS formulations over a 10 h observation period are presented in the table. Evaluation of ITZ release from the prepared SNES is essential for predicting in vivo performance and ensuring adequate drug release and absorption. As shown in the figure, formulation IS5 exhibited a markedly faster release compared with the other formulations, which may be attributed to improved drug solubilization, smaller globule size, lower PDI, and shorter self-emulsification time.

Table 7. Cumulative Drug release (%) of various ITZ SNEDDS Batches

Times	IS1	IS2	IS3	IS4	IS5	IS6	IS7	IS8	IS9
0.5	39.01	35.02	38.02	32.02	50.28	39.02	45.02	42.02	45.02
1	40.42	39.52	39.03	37.03	53.38	42.03	48.03	47.03	48.03
2	43.23	40.25	41.23	38.23	55.07	48.23	52.23	48.23	51.42
4	48.59	45.23	45.25	42.25	57.32	51.25	58.25	52.25	53.25
6	55.07	50.26	52.26	48.26	66.90	54.26	64.26	58.26	58.26
8	62.85	55.25	59.24	53.24	77.32	59.24	69.24	63.24	63.24
10	68.02	65.26	67.00	62.00	84.36	69.00	72.00	69.00	69.50

*All values are in percentage

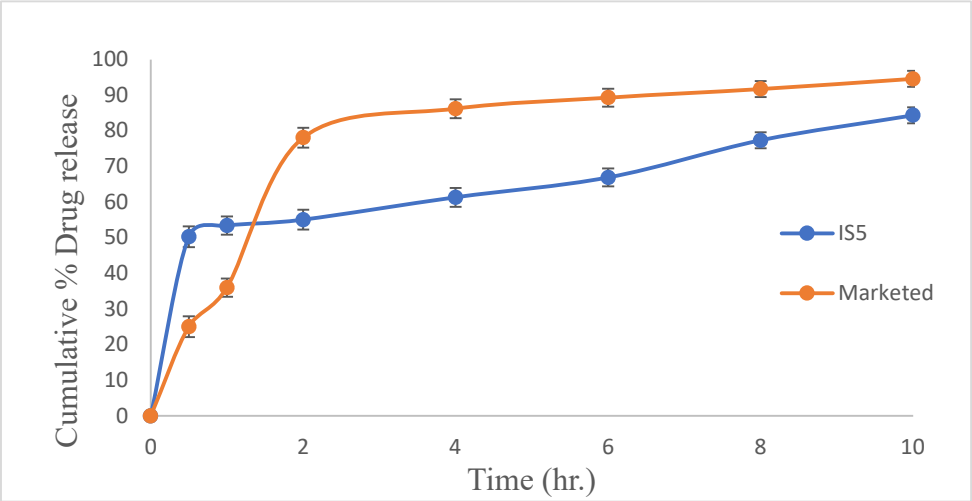
Figure 6: *In vitro* release profile of selected SNEDDS formulations through dialysis membrane.



COMPARATIVE *IN-VITRO* DRUG RELEASE STUDY BETWEEN MARKETED AND IS5 BATCH

Comparative diffusion testing revealed that ITRAL (1% w/v) released 97.58 ± 2.25 % itraconazole within 10 hrs depicted and shown in figure 4. The eye drop releases drug immediately through dialysis membrane. It might due to the less viscosity of ITRAL (1% w/v) compared to IS5 shown sustained drug release. Dialysis membrane filter acts as a mechanical barrier to drug diffusion.

Figure 7: Comparative *In-Vitro* Drug release study between marketed and IS5 batch



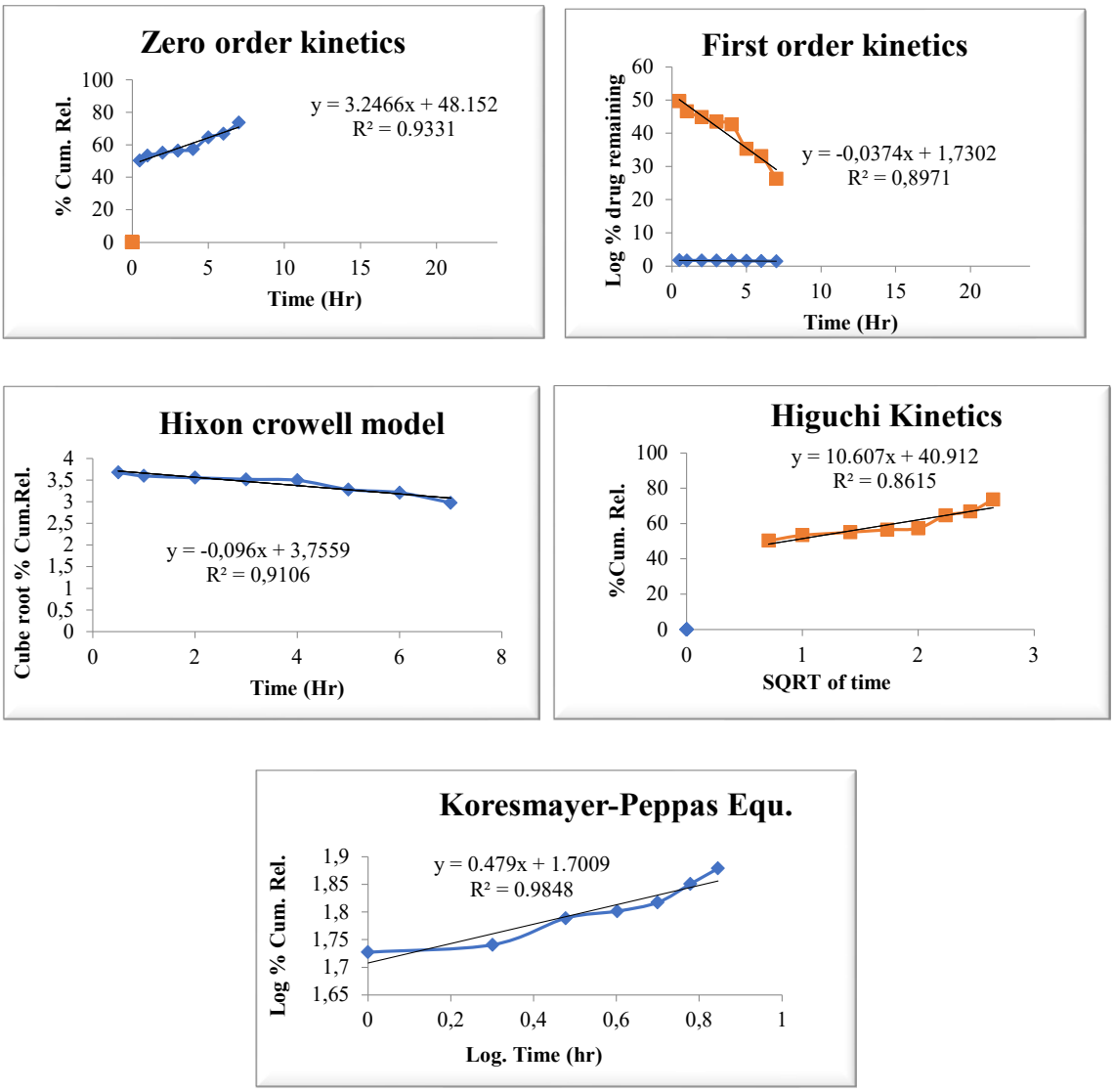
DRUG RELEASE KINETICS MODELLING

The slopes and R^2 values derived from fitting in vitro diffusion data to the Korsmeyer–Peppas model are displayed as a log–log plot of cumulative percentage drug released against time.

The *in-vitro* release kinetics of all itraconazole-loaded SNEDDS formulations were evaluated, and the regression coefficients (R^2) for the optimized IS5 batch were determined using various kinetic models.

Among the kinetic models evaluated -: zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell, the ITZ release data from SNEDDS best conformed to the Higuchi square-root model, as indicated by the highest R^2 value. The release exponent (n) obtained from the Korsmeyer–Peppas model fell between 0.43 and 0.85, consistent with anomalous (non-Fickian) transport governed by a synergy of diffusion and matrix swelling-dissolution.

Figure 8: Koresmayer-Peppas release kinetic model of selected SNEDDS



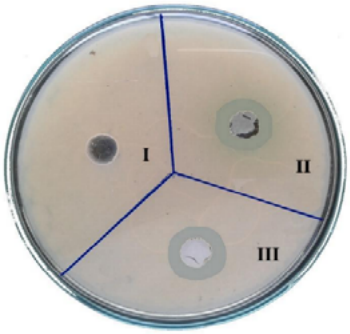
IN VITRO ANTIFUNGAL ACTIVITY

The antifungal activity was assessed using the agar well diffusion assay. Itraconazole-loaded SNEDDS demonstrated notably superior inhibitory efficacy against *Candida albicans* compared to the marketed formulation ITRAL (1% w/v). The average diameters of the inhibition zones against *Candida albicans* are presented in the table and illustrated in the corresponding image.

Table 8. Comparative *In vitro* antifungal activity

Sr no.	Solution	Zone of inhibition (mm)
I	SNEDDS without drug	5
II	ITRAL (1% w/v)	14
III	IS5 Formulation	13

Figure 9: Comparative antifungal study of itraconazole loaded Self-Nanoemulsifying drug delivery system



DISCUSSION

Solubility of itraconazole was systematically assessed in various oils to identify the most appropriate lipophilic phase for constructing a nanoemulsion-based delivery system. Enhanced solubility noted in oleic acid and isopropyl myristate can be explained by their strong lipophilic characteristics and penetration-enhancing effects, which promote improved drug dissolution. Notably, blending oleic acid with isopropyl myristate produced a synergistic enhancement in drug solubility (2.46 ± 0.05 mg/ml) compared to the individual oils. This synergistic effect suggests improved solubilization capacity due to better molecular interactions between the drug and the mixed oil phase. Hence, the oil blend was considered more suitable for incorporation into the nanoemulsion system. Prudent selection of surfactants and co-surfactants is essential in ocular nanoemulsion development, since only a few are recognized as safe and non-irritating for ophthalmic application. Non-ionic surfactants are typically favoured because of reduced toxicity and enhanced ocular compatibility. In the present study, itraconazole showed higher solubility in Tween 80 (2.26 ± 0.18 mg/ml) compared to other surfactants, while propylene glycol demonstrated comparatively higher solubility among the co-surfactants (1.85 ± 0.11 mg/ml). Tween 80 and polyethylene glycol 400 possess HLB values of 15 and 20, respectively, which are well-suited for stabilizing oil-in-water (o/w) nanoemulsion systems, which are preferred for ocular delivery. Overall, solubility assessment provided a scientific rationale for selecting the oil phase, surfactant, and co-surfactant, a critical step toward achieving higher drug loading and a stable nanoemulsion appropriate for ocular administration.

Among the tested combinations, the oil: Smix ratio of 1:9 exhibited superior transparency upon aqueous dilution, indicating efficient self-nanoemulsification and formation of a stable o/w nanoemulsion. A 1:1 proportion of Tween 80 to PEG 400 was determined as optimal for efficient emulsification. Based on these observations, the 1:9 oil to Smix ratio was selected for further factorial design optimization.

The droplet size analysis of the formulated ITZ-SNEDDS revealed mean particle sizes below 100 nm for all batches, which is desirable for ocular delivery due to better tolerability and enhanced drug permeation. The size of a droplet was minimal with maximal surfactant concentration also, decreasing oil content, indicating efficient self-nanoemulsification and improved interfacial stabilization. Such nanosized droplets are expected to provide higher surface area and improved ocular bioavailability. Zeta potential studies showed that all formulations possessed negative surface charges ranging from −10.2 to −18.6 mV, suggesting adequate physical stable capacity of the nanoemulsion system. An negative zeta potential is ascribed to the steric stabilization conferred by the non-ionic surfactant Tween 80 and co-surfactant PEG 400, rather than conventional electrostatic mechanisms. Overall, the droplet size and zeta potential results, suitability and stability of the developed ITZ-Delivery system for ophthalmic application. The PDI serves as a critical index of droplet size uniformity and is closely linked to the physical stability of nanoemulsion formulations. In the present study, all ITZ-SNEDDS formulations exhibited PDI values below 0.7, ranging from 0.416 to 0.515, indicating a relatively narrow and uniform droplet size distribution. Such PDI values suggest effective self-emulsification and homogeneity of the nanoemulsion system. The limited size distribution observed, as illustrated in the table and graphical representation, confirms the formation of stable SNEDDS with minimal droplet aggregation. Overall, the acceptable PDI values demonstrate good physical stability of the developed ITZ-SNEDDS formulations.

Emulsification duration functions as a critical indicator of SNEDDS performance, representing how efficiently the preconcentrate converts into a uniform

nanoemulsion when exposed to an aqueous medium. In the present study, emulsification time was recorded by visually tracking the complete disappearance of the SNEDDS preconcentrate and the emergence of a clear, uniform nanodispersion. All formulations exhibited rapid and complete self-emulsification in aqueous media, indicating efficient dispersion and good formulation performance. The short emulsification time observed, as presented in Table, confirms the suitability of the developed SNEDDS for immediate nanoemulsion formation, which is desirable for ocular drug delivery.

Drug loading analysis confirmed that all prepared ITZ-SNEDDS batches contained itraconazole within the acceptable range, indicating uniform drug distribution within the system. The formulations exhibited drug content values ranging from 87.35 ± 1.2% to 89.63 ± 1.2%, as presented in the table and graphical representation. Notably, formulations IS5, IS6, and IS7 showed comparatively higher drug content, exceeding 90%, which reflects efficient drug incorporation and minimal drug loss during formulation. These results confirm the reproducibility and reliability of the SNEDDS preparation method and support the suitability of the selected formulations for further evaluation.

Viscosity is an important parameter for the physical characterization and stability assessment of SNEDDS, as it directly influences dispersion behaviour and emulsification efficiency. In the present study, viscosity measurements were carried out at 25 ± 0.5 °C using a Brookfield viscometer. All SNEDDS formulations exhibited optimum viscosity values, as shown in the table, which are suitable for rapid self-emulsification upon aqueous dilution. The observed viscosities were low enough to ensure efficient dispersion while avoiding delayed emulsification that could adversely affect drug release and bioavailability.

The pH of ophthalmic formulations plays a critical role in ocular comfort and safety. The prepared SNEDDS formulations showed pH values ranging from 5.89 ± 0.11 to 6.39 ± 0.12, which fall within the acceptable ocular pH range. Such values are unlikely to cause irritation or corneal damage, as the eye's natural buffering capacity can readily accommodate minor pH variations. Therefore, the pH of the developed SNEDDS is considered suitable for ocular administration, with minimal disturbance to normal tear physiology.

Dilution stability is a critical requirement for SNEDDS intended for drug delivery, as the formulation must remain stable upon extensive aqueous dilution without exhibiting drug crystallization or phase separation. In the present study, all ITZ-SNEDDS formulations were evaluated for their behaviour upon dilution. The diluted nanoemulsions remained visually transparent and clear, with no sign of phase separation throughout the 24 h evaluation period, indicating good thermodynamic stability. Such behaviour is particularly desirable for ocular application, as stable emulsified oil globules can readily spread over the ocular surface without compromising formulation integrity. However, slight instability upon aqueous dilution was observed with formulations IS1, IS4, and IS7. Overall, the findings suggest that most ITZ-SNEDDS formulations exhibited satisfactory dilution stability, supporting their suitability for ocular drug delivery.

A progressive time-dependent release of itraconazole was observed across all ITZ-SNEDDS formulations during the in vitro diffusion study. A gradual and sustained release pattern was observed over 10 h, indicating effective drug solubilization and controlled release behaviour. Among all formulations, IS5 showed the highest cumulative drug release at each time point, reaching about 84.36% at 10 h, which may be attributed to its optimized oil–surfactant–co-surfactant composition and smaller droplet size. Formulations IS7, IS8, and IS9 also exhibited comparatively higher drug release profiles than the remaining batches. Overall, the results confirm that SNEDDS significantly enhance the dissolution and release of itraconazole, with IS5 emerging as the most promising formulation for ocular delivery.

The zero-order kinetic plot of % cumulative drug release versus time exhibited a good linear relationship with a regression equation $y = 3.2466x + 48.152$ and a high correlation coefficient ($R^2 = 0.9331$), indicating a near constant drug release rate over the studied time period. The slope of the plot (3.2466 $\%\cdot h^{-1}$) represents the zero-order release constant, suggesting controlled and predictable drug release from the formulation. The near zero-order release observed can be attributed to the **SNEDDS-based system**, which upon contact with the aqueous dissolution medium forms a stable Nano emulsion. The presence of Nano-sized dro-

plets provides a large surface area for drug diffusion while maintaining drug solubilization, thereby preventing rapid drug precipitation and burst release.

The first-order kinetic plot showed a good linear relationship between log % drug remaining and time with the regression equation $y = -0.0374x + 1.7302$ and a high correlation coefficient ($R^2 = 0.8971$), confirming concentration-dependent release of itraconazole from the developed system. concentration-dependent. The negative slope confirms a progressive decrease in drug concentration with time, which is characteristic of diffusion-driven release systems. Overall, the good fit to the first-order model supports the role of SNEDDS in modulating itraconazole release through controlled diffusion from Nano emulsion droplets, contributing to improved ocular availability and prolonged therapeutic action.

The Hixson Crowell kinetic plot exhibited good linearity with the regression equation $y = -0.096x + 3.7559$ and a high correlation coefficient ($R^2 = 0.9106$), confirming that drug liberation from the system correlates with progressive changes in changes in surface area and particle size during dissolution. This suggests that the release of itraconazole is influenced not only by diffusion but also by structural reorganization of the formulation. The good fit to the Hixson–Crowell model confirms that SNEDDS maintains controlled drug release through dynamic changes in droplet structure.

Higuchi kinetic plot showed good linearity ($R^2 = 0.8615$), indicating that the release of itraconazole from the formulation is predominantly governed by diffusion-controlled mechanisms. This behaviour is characteristic of SNEDDS systems, where rapid formation of Nano emulsion droplets upon aqueous dilution generates an expansive interfacial surface area that promotes effective drug diffusion into the surrounding dissolution medium. The Higuchi fit confirms that diffusion from Nano-sized droplets plays a major role in sustaining drug release.

The Korsmeyer–Peppas plot demonstrated an excellent correlation ($R^2 = 0.9848$) with a release exponent $n = 0.479$, suggesting a quasi-Fickian to anomalous diffusion mechanism. This indicates that drug release is controlled primarily by diffusion with a minor contribution from structural rearrangement of the SNEDDS matrix. Such a release mechanism is advantageous for ophthalmic delivery, as it ensures controlled drug diffusion without an excessive burst effect.

The comparative in vitro release study showed that the marketed formulation ITRAL (1% w/v) released 97.58 ± 2.25% of itraconazole within 10 h, as depicted in Figure 4. The rapid drug release from ITRAL can be attributed to its lower viscosity, which allows immediate diffusion of the drug through the dialysis membrane. In contrast, the optimized SNEDDS formulation (IS5) exhibited a sustained release profile, likely due to its higher viscosity and nanoemulsion structure that modulates drug diffusion. The dialysis membrane served as a physical diffusion barrier, thereby modulating the permeation rate of itraconazole. Overall, the sustained release behaviour of IS5 suggests its potential advantage over the conventional eye drop in prolonging ocular drug availability.

The antimicrobial activity study revealed distinct differences in the zone of inhibition among the tested samples. SNEDDS without drug showed a minimal zone of inhibition (5 mm), indicating negligible inherent antimicrobial activity of the excipients. The marketed formulation ITRAL (1% w/v) exhibited the largest zone of inhibition (14 mm), reflecting its immediate drug availability and rapid diffusion. The optimized IS5 formulation demonstrated a comparable zone of inhibition (13 mm), suggesting effective antifungal activity of itraconazole despite its sustained release behaviour. These results confirm that the SNEDDS formulation retains the therapeutic efficacy of itraconazole while offering the added advantage of controlled drug release, making IS5 a promising system for ocular antifungal delivery.

CONCLUSION

This study successfully developed an Itraconazole-loaded SNEDDS optimized for ocular drug delivery using a 3^2 factorial design. The optimized formulation demonstrated favourable attributes, including diminished droplet size, suitable zeta potential, high drug loading, rapid self-emulsification, and improved in vitro drug release. Comparative diffusion studies showed superior release performance compared to the marketed formulation, indicating enhanced therapeutic potential. Furthermore, the antifungal efficacy of the

developed system was significantly greater than that of the commercial product. Overall, these results highlight SNEDDS as a promising approach for enhancing ocular delivery of poorly water-soluble antifungal drugs. Further *ex vivo* and *in vivo* investigations are warranted to confirm its clinical applicability. To conclude, this investigation suggests that SNEDDS offers a promising and efficient approach for enhancing the ocular delivery of poorly water-soluble antimycotic agents like itraconazole. The optimized formulation may enable reduced dosing frequency, improved patient adherence, and enhanced therapeutic outcomes in managing ocular fungal infections. Nevertheless, comprehensive *ex vivo* corneal permeability studies and *in vivo* ocular pharmacokinetic and safety evaluations are necessary to substantiate its clinical relevance and translational feasibility.

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