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Formulation of Itraconazole Loaded Clove Oil based Nanoemulsion using Pseudoternary Phase Diagram for Improved Thermodynamic Stability

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The present study focuses on formulating, developing, and characterizing nanoemulsions (NE) of antifungal drug (Itraconazole) for its better thermodynamic stability. This way it is expected to be better utilized as a carrier for the transdermal delivery of the drug against Candida albicans infection. The solubility of the drug in various oils was investigated, leading to the identification of an oil phase (clove oil) that not only met the desired solubility criteria but also is reported to exhibit an antifungal effect. The subsequent step involves constructing a pseudo-ternary phase diagram and performing associated mathematical calculations to achieve a thermodynamically stable NE, utilizing the titration method at a constant temperature. The 4:1 ratio of Smix (a mixture of polysorbate 80 as a surfactant and polyethylene glycol 400 as a co-surfactant) was selected based on the largest area of transparency. This study aims to give an insight into the importance of pseudo ternary phase diagram construction and its evaluation, as a significant means for the development of NE. Furthermore, the optimized formulation was chosen and evaluated for key parameters, such as droplet size, polydispersity index, zeta potential, and viscosity. The results exhibited promising characteristics in terms of droplet size and zeta potential indicating the stability of the formulation which can be further explored for suitable dermal drug delivery.

Keywords: Antifungal; Candida albicans; Nanoemulsion; Pseudo ternary phase diagram; thermodynamic stability

1 Introduction

Itraconazole (ITZ) serves as an antifungal agent having broad spectrum activity against Candida species, However, ITZ exhibits low solubility in water (BCS Class-II drug), specifically 4 µg/mL at pH 1, with a log P value of 5.66 and pKa of 3.7. Additionally, ITZ displays pH-dependent solubility, showing low solubility (at alkaline pH),low thermodynamic stability with high solubility at acidic pH[1]. With a melting point of 167 °C, it is fungistatic at all concentrations against clinical isolates of Candida albicans, rendering it a suitable drug of choice[2]. For patients resistant to fluconazole, drugs like Voriconazole and ITZ can serve as alternative therapies[3]. The antifungal effect of ITZ arises from the inhibition of cytochrome P-450 enzymes, limiting the demethylation of lanosterol crucial for ergosterol synthesis. This suppression alters the membrane permeability of the fungus, resulting in an antifungal effect. By incorporating ITZ into nanoemulsions (NE), we are expecting that ITZ's solubility, thermodynamic stability and bioavailability at the target site will improve serving as an effective carrier for this hydrophobic drug.

NEs are heterogeneous compositions of two different immiscible fluids, which are usually oil-water mixtures that are stabilized with surfactants and co-surfactants[4]. In this form, they offer better functional properties compared to conventional emulsions. ITZ-loaded NEs have been mentioned in previous reports[5-7]. Microemulsions containing ITZ and clove oil have been prepared previously, but our work focuses on the pseudo-ternary phase diagram, formulation, and further optimization of ITZ-loaded clove oil-based NEs to check their thermodynamic stability for the best possible droplet size, PDI and zeta potential.

One crucial factor in determining how well this drug delivery systems work is NE stability. Pseudo-ternary phase diagrams are therefore crucial for creating a thermodynamically stable emulsion. Ternary diagrams for emulsions are usually determined by the time-consuming method of solubility and water titration (drop method)[8]. In this method, a mixture consisting of an oil phase and an amount of emulsifier determined by the Smix value is titrated with the aqueous phase drop wise until the mixture is isotropic (clear, homogeneous). The

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isotropy of the mixture (with transparent systems less than 150 nm) together with the homogeneity of the multicomponent system is observed with visual inspection[9]. In an additional step, the aqueous phase is added and titrated with a mixture of oil and emulsifier until isotropy is achieved. To increase emulsion stability, we can optimize and define a stable phase range for mixing. Phase diagrams can predict the type of emulsion formed, their miscibility, phase behavior, globule size, and thermodynamic stability. Based on the predictions of the phase diagram, the ideal ratio of water phase, oil phase and surfactant concentration can be achieved. The phase diagram offers the advantage of the ability to predict the range of working concentrations of various surfactants, as well as the main mechanisms of action, including bicontinuous, lamellar, and reverse micellar concentrations[10].

In addition, the use of clove oil as nanoemulsion's oil phase is expected to provide a synergistic effect due to its inherent antifungal activity[11-13]. It also acts as a skin penetrant by disrupting the subcutaneous intercellular lipids[14]. The prepared optimized NEs were evaluated for droplet size, zeta potential, PDI and viscosity. This study is an attempt to study clove oil as an oil; polysorbate 80 as a surfactant; and PEG 400 as co-surfactant, which are expected to enhance drug solubility for better absorption. However, no such systematic study has been previously reported. This will enable an effective, optimized, thermodynamically stable and transparent antifungal NE using a simple, low-cost and scalable methodology.

2 Material and Methods

2.1 Materials

ITZ was received as a gift sample from Intas Biopharmaceutical Ltd, Ahmedabad, India. Clove oil was obtained from the Central Drug House (CDH). Other chemicals such as polysorbate 80 used as surfactant, polyethylene glycol (PEG 400) used as co-surfactant were purchased from Research Fine Chem Pvt. Ltd., Mumbai, India, and were of suitable analytical grade. Freshly prepared double-distilled water was used in the entire experiment.

2.2 Methods

2.2.1 Analytical method development and Standard Calibration Curve of Itraconazole in methanol

A UV spectrophotometer was used to quantify the Active Pharmaceutical Ingredient (API).

The APIs actually is the main ingredient that possess pharmacological activity which are used alone or in combination with other active components to diagnose, cure, alleviate, and treat various diseases or body conditions[15]. The absorbance of the solutions was measured using a pair of quartz cells. For reference and test solutions, absorption spectra were obtained in the 200–400 nm range. In addition, a calibrated digital balance was used to accurately weigh 10 mg of drug (ITZ), which was then transferred to a 100 mL volumetric flask. A small amount of methanol is added to dissolve the drug. The volume was brought up to 100 mL using methanol to prepare a 100 µg/mL stock solution. From the original solution, 0.2, 0.4, 0.6, 0.8 and 1.0 ml of the solution were poured into 10 ml volumetric flasks with a pipette and the volume was brought up to 10 ml with the formation of concentrations 2, 4, 6, 8 , 10 (µg/ml) with methanol. Absorbance was measured using a UV spectrophotometer at 262 nm using methanol as a reference solution. All studies are performed in triplicate (n = 3)[16].

2.2.2 Drug solubility analysis in various oils

It is very important to ensure the maximum solubility of ITZ in the oil phase of NE as it is a poorly soluble drug. Thus, to obtain good stability for effective dermal delivery of ITZ,its solubility was measured in a variety of oils *i.e*. Thuja, Tea Tree, Cinnamon, Mentha, Peppermint, Nutmeg, Jojoba, Chamomile, Clove, Rosemary, Grapeseed, Hibiscus, Cedarwood and Lavender oil taken in vials using shake flask method. Beiefly, an excess amount of ITZ was added to 1 ml of oil individually followed by vortexing using vortex mixer (GeNei, Bangalore, India) for 5 minutes. In addition, the vials were placed on a shaking water bath (iGeneLabserve) for 72 hours at 37 °C and a speed of 300 rpm. A high-speed centrifuge (Remi Laboratory Instruments, Mumbai, India) was used to centrifuge each vial for 10 minutes at 10,000 rpm. All the samples were subsequently diluted with methanol. Amount of drug present in each sample was determined using UV Visible spectrophotometer (UV-1700, Shimadzu Corporation, Tokyo, Japan) set at 262 nm. The study was performed in triplicate and the absorbance values were recorded for further statistical treatments[17].

2.2.3 Selection of surfactant and co-surfactant

For ITZ NE formulation, four surfactants Span 80, Tween 20, Tween 60, and Tween 80were screened.

For screening, 2.5 mL of 15 wt.% surfactant solution in water was prepared, and 4 µL of oil was added to them individually with vigorous vortexing to produce a single-phase clear solution. A surfactant with a Hydrophilic Lipophilic Balance (HLB) value greater than 11 was chosen for the preparation to obtain a transparent and stable oil in water NE. The HLB value is an indication of the equilibrium between the hydrophilic and lipophilic components in a surfactant molecule and indicates its size and strength. The HLB scale, ranging from 0 to 20, guides the selection of surfactants for specific emulsion types. Surfactants with HLB values within the 3.5 to 6.0 range are better suited for W/O emulsions, while those falling between 8 and 18 are commonly employed in O/W emulsions, as proposed by Griffin in 1949[18].

Selected surfactant was further combined with six different solubilizers individually as cosurfactants (ethanol, isopropyl alcohol, n-butanol, PEG 400, PEG 200, and propylene glycol) to test their compatibility for a stable Smixin combination with the selected surfactant. The oils were then mixed with surfactants that were compatible to test the oils' miscibility. The mixture's stability was observed visually under various time intervals and conditions. For seven days, samples were incubated at 37 and 50 °C. Samples that remained stable for a period of seven days were chosen for aqueous phase titration to create a pseudo-ternary phase diagram that can be used to govern NE development[19].

2.2.4 Pseudo-ternary phase diagram construction

Triplot version 4.1 was used for the construction of the pseudo ternary phase diagram. It was also useful in characterizing NE behavior using dilution technique. The surfactant and co-surfactant combinations (Smix) were added in the following ratios: 1:0, 1:1, 1:2, 1:3, 3:1, 2:1, 4:1, and 1:4. Water was added while stirring constantly until turbidity developed, and the volume of water consumed was measured to produce clear or translucent NE. The mass percentages of water, surfactant/co-surfactant, and oil were reported as these endpoints with the sum of 100% [21]. Plotting the final formulations against the ratios of oil, water, and Smix resulted in a ternary phase diagram[22,23].

2.2.5 Preparation of ITZ loaded NE

ITZ-loaded NE was created by using blank NE with a low Smix ratio that contained water (95.24%), Smix (4.29%), and oil (0.47%). To create NE, components of the chosen blank NE were combined with 1% ITZ. Briefly, ITZ was dissolved in the oil phase. Subsequently, Smix and the aqueous phase were introduced gradually and mixed according to the above ratio[24].

2.2.6 Studies on Thermodynamic Stability

Thermodynamic stability tests were carried out to solve the metastable formulation issue. For 30 minutes, the chosen formulation was centrifuged at 3500 rpm. In addition, the formulation was heated and cooled six times for 48 hours at 4 and 45 °C. A freeze-thaw cycle was also used to test the optimal NE. The material was placed in a vial and frozen at -4 °C for 12 hours. The NE was thawed for an additional 12 hours at room temperature. The studies were performed in triplicate. An assessment was conducted using cross-polarized light to look for potential phase separation[25].

2.2.7 Zeta Potential, PDI, and droplet size measurement

Using Malvern Zetasizer (Nano ZS, 90, UK), the mean globule size and PDI of ITZ-clove oil containing NE were measured. For greater accuracy, the NE batch (0.1 mL) was diluted with 10 mL of double-distilled water and subjected to triplicate testing for zeta potential and globule size[26].

2.2.8 Viscosity measurement

Without any dilution, the viscosity of the optimised batch was measured using a Brookfield viscometer (DV-II+ Pro). At 30 degrees Celsius, the viscosity of the prepared formulations was measured using spindles no. 1 and 2. The values were taken after the spindle was set at 30 rpm for 1 minute. The measurements were performed in triplicate[27,28].

3 Results and Discussion

3.1 Analytical method development and Standard Calibration Curve of Itraconazole in methanol

On scanning in 200-400nm range, the concentration of (2µg/ml) of ITZ displayed maximum absorbance at 262 nm (Fig. 1(a)), which is in compliance with the earlier reports. It was found that the ITZ was linear in the concentration range of 2–10 µg/ml, with a regression equation of y = 0.0754x - 0.0142 and a regression coefficient of 0.998by the absorbance ratio method. An excellent correlation between absorbance and concentration was observed as shown in Fig. 1(b).

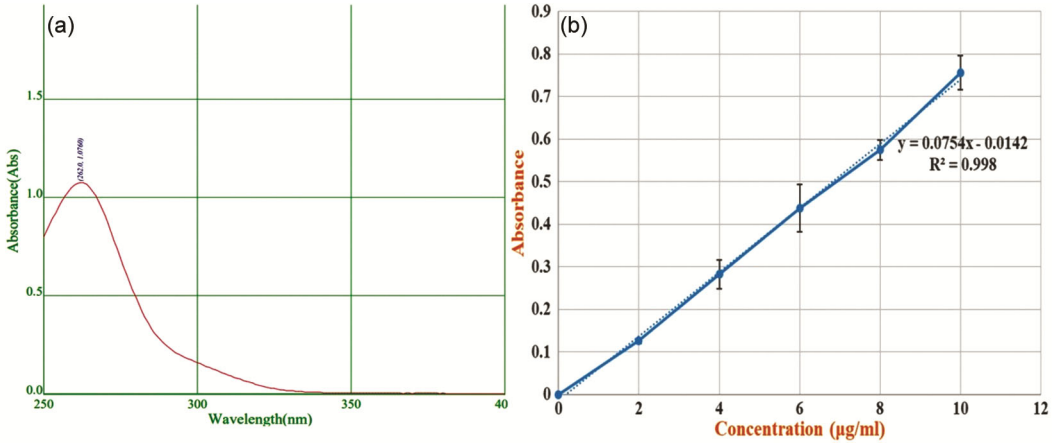

Figure 1 — (a) UV spectrum of Itraconazole and (b) Calibration curve of ITZ in methanol

Table 1 — Solubility determination of ITZ in oils

S.No.	Name of oil	Solubility (mg/ml)
1	Thuja	0.61 ± 0.21
2	Tea Tree	0.82 ± 0.04
3	Cinnamon	63.24 ± 0.02
4	Mentha	0.33 ± 0.17
5	Peppermint	0.95 ± 0.52
6	Nutmeg	0.42 ± 0.64
7	Jojoba	0.72 ± 0.26
8	Chamomile	0.07 ± 0.32
9	Clove	53.45 ±0.04
10	Rosemary	0.12 ± 0.28
12	Grapeseed	0.34 ± 0.36
13	Hibiscus	0.08 ± 0.38
14	Cedarwood	0.63 ± 0.67
15	Lavender	0.49 ± 0.06

3.2 Drug solubility analysis in various oils

The drug's solubility was assessed in Thuja, Tea Tree, Cinnamon, Mentha, Peppermint, Nutmeg, Jojoba, Chamomile, Clove, Rosemary, Grapeseed, Hibiscus, Cedarwood and Lavender oil by shake flask method. The results obtained are shown in Table 1. The highest solubility of ITZ was found to be 63.24 ± 0.02 mg/ml in cinnamon oil. However, clove oil was chosen as the oil phase having 53.45 ±0.04 mg/ml solubility for the drug as the droplet size with cinnamon oil-based emulsion was found to be very large *i.e.* >1000 nm which is not in the nanoscale range. The inherent antifungal activity of clove oil expecting a synergistic anti-fungal effect was an additional reason of choosing clove oil as oil phase in the nanoemulsion.

3.3 Selection of surfactant and co-surfactant

The choice of an appropriate oil and Smix have a major impact on the formulation of a stable NE. The oil phase facilitates the solubilization of drug molecules and the surfactants' mixture reduce the interfacial tension Depending on the interfacial dynamics, phase behavior, viscosity and interfacial tension, the oil phase affects the initial NE droplet size. In addition, formulation stability is affected by the polarity of oil phase components, which also has a significant effect on NE droplet size during storage[29]. Therefore, it is critical to determine an appropriate oil phase composition that promotes a stable, long-term NE system. After thorough investigations into the drug's solubility and the oil compatibility of several Smix, the oil phase was selected. In the present, clove oil was selected for NE preparation based on solubility studies[30].

Tween 80 and PEG 400 were selected as the surfactant and co-surfactant, respectively, based on a compatibility study. At the chosen concentration used, Tween 80 was suitable for the study because it is hydrophilic, non-toxic and has reported HLB value of 15. Compared to their ionic counterparts, nonionic surfactants in O/W NEs can lead to greater stability and less toxicity[31].

The use of surfactants alone is not enough to reduce surface tension, so cosurfactants are also added whose function here is to improve the film flexibility[32]. The cosurfactant PEG 400, a mid-chain hydrocarbon having two hydroxyl and relatively short ethylene groups and is used in the present study. It is expected to be placed between gaps in NE systems through the formation of hydrogen chains. This process will maximize the emulsification process by reducing the interfacial tension and improving the fluidity of the interface by reducing bending stress which is helpful to develop a stable NE preparation[33].

The area of the stable NE region in the pseudo-ternary phase diagram was found to increase with the addition of co-surfactant. Since co-surfactant can increase the fluidity and film-breaking effect of the surfactant, their use is expected to promote single-phase emulsions[34,35]. Further, PEG 400 could provide a linkage between the hydrophobic and hydrophilic phases[36]. As a co-surfactant, PEG 400 compliment the function of Tween 80 in reducing the water-oil interfacial tension. The two hydroxyl and short ethylene groups can penetrate the interfacial area and form a compact layer of surfactant-cosurfactant[37]. This further allows a wide range of curvature to be achieved, increasing the monophasic area[38,39]. Because PEG 400 is compatible with Tween 80, it was chosen as a co-surfactant.

3.4 Pseudo-ternary phase diagram construction

A stable NE is a function of its system composition. The NE formation zone can be illustrated using a pseudo-ternary phase diagram. However, the mixing order of the different components is not expected to affect NE formation if the system is indeed thermodynamically stable form[20].

NE formulations were prepared by changing the weight ratio of the Smix in 1:0, 1:1, 1:2, 1:3, 3:1, 2:1, 4:1, and 1: 4 ratios to find their transparent zone. While constructing the phase diagram, we first determined the mass ratio of surfactant (Tween 80) and cosurfactant (PEG 400). This selected ratio was fixed at a constant level throughout the measurement. In pharmaceutical applications, this oil in water type NE encapsulated the hydrophobic drug itraconazole and was able to accommodate larger amount of water. The titration method was used at constant temperature for constructing the pseudo-ternary phase diagram. For this system consisting of Tween 80, PEG 400, clove oil and water, the NE phase was observed to be a homogeneous, transparent, and stable phase with the maximum area of transparency at a Smix ratio of 4:1. The calculations and percentage of components used for the construction are shown in Table 2.

Pseudoternary phase diagram of the surfactant and cosurfactant (Smix) mixture ratios (1:0, 1:1, 1:2, 1:3, 1:4 and 2:1) oil/water nanoemulsion are shown in Fig. 2 and Smix ratios (3:1, and 4:1) oil/water nanoemulsion are shown in Fig. 3. The dots pattern are representing the region of transparency. The other Smix ratios *i.e.* 1:2, 1:3 and 1:4 failed to show the areas of transparency. A low transparency region was observed when the Smix was at 1:0, 1:1, 2:1, and 3:1 ratios as shown in Figs. 2 & 3. Thus, it can be concluded that PEG 400 plays a major role in maximizing the transparency area at a 4:1 ratio. However, at higher concentrations, its effect shows lesser or no transparency.

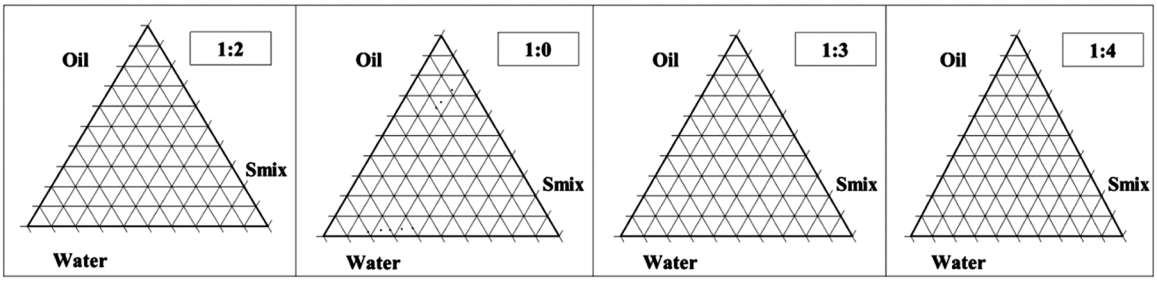

Fig 2 — Pseudoternary phase diagram of the surfactant and cosurfactant (Smix) mixture ratios (1:0, 1:1, 1:2, 1:3, 1:4 and 2:1) Oil/water nanoemulsionwhere the dots pattern are representing the region of transparency

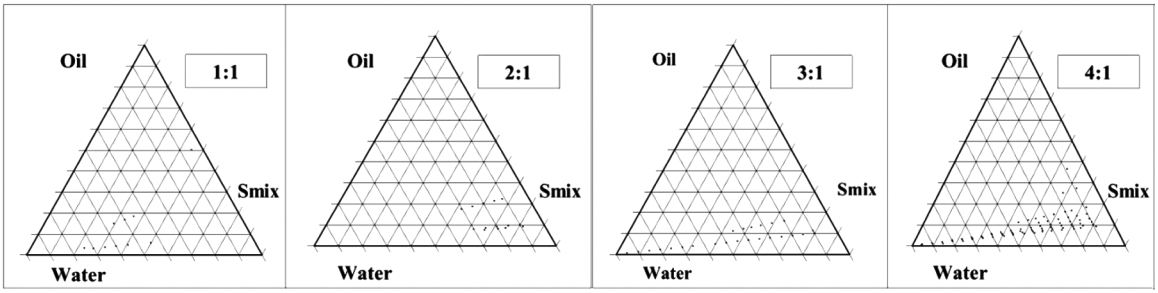

Fig 3 — Pseudoternary phase diagram of the surfactant and cosurfactant (Smix) mixture ratios (3:1, and 4:1) Oil/water nanoemulsion where the dots pattern are representing the region of transparency

Table 2 — Percentage of Oil, Surfactant, and Water Used in Phase Diagram Construction Calculation (Smix is in 4:1 ratio)

Sample	Proportion (%)			Sample	Proportion (%)		
no.	Oil	Smix	Water	no.	Oil	Smix	Water
1	10	80	10	42	6.41	38.46	55.13
2	9.43	75.48	15.09	43	5.71	34.29	60.00
3	8.89	71.11	20.00	44	14.93	74.63	10.44
4	8.33	66.67	25.00	45	14.08	70.43	15.49
5	7.75	62.02	30.23	46	13.33	66.67	20.00
6	7.22	57.76	35.02	47	12.50	62.50	25.00
7	6.67	53.33	40.00	48	11.56	57.80	30.64
8	6.12	48.93	44.95	49	10.81	54.05	35.14
9	5.56	44.44	50.00	50	36.36	54.55	9.09
10	5.00	40.00	55.00	51	27.27	63.64	9.09
11	3.88	31.07	65.05	52	25.00	58.33	16.67
12	3.33	26.67	70.00	53	18.18	72.73	9.09
13	2.78	22.22	75.00	54	16.66	66.67	16.67
14	2.22	17.78	80.00	55	16.00	64.00	20.00
15	1.67	13.33	85.00	56	14.81	59.26	25.93
16	1.11	8.89	90.00	57	9.09	81.82	9.09
17	0.56	4.44	95.00	58	8.33	75.00	16.67
18	11.24	78.65	10.11	59	8.00	72.00	20.00
19	10.53	73.68	15.79	60	7.40	66.67	25.93
20	10.00	70.00	20.00	61	6.90	62.07	31.03
21	9.35	65.42	25.23	62	6.46	58.06	35.48
22	8.70	60.87	30.43	63	6.06	54.55	39.39
23	8.13	56.91	34.96	64	5.56	50.00	44.44
24	7.49	52.44	40.07	65	5.00	45.00	50.00
25	6.78	47.46	45.76	66	4.55	40.91	54.54
26	6.25	43.75	50.00	67	4.00	36.00	60.00
27	5.62	39.32	55.06	68	3.51	31.58	64.91
28	5.00	35.00	60.00	69	2.99	26.87	70.14
29	4.35	30.43	65.22	70	2	23	75
30	3.74	26.17	70.09	71	2.00	18.00	80.00
31	3.13	21.87	75.00	72	1	14	85
32	2.50	17.50	80.00	73	1.00	9.00	90.00
33	12.82	76.92	10.26	74	0.47	4.29	95.24
34	12.12	72.73	15.15	75	18.18	72.73	9.09
35	11.43	68.57	20.00	76	16.67	66.67	16.66
36	10.70	64.17	25.13	77	16.00	64.00	20.00
37	10.00	60.00	30.00	78	14.81	59.26	25.93
38	9.26	55.56	35.18	79	13.79	55.17	31.04
39	8.58	51.50	39.92	80	12.90	51.61	35.49
40	7.84	47.06	45.10	81	12.13	48.48	39.39
41	7.14	42.86	50.00	82	11.12	44.44	44.44

Proper selection of the type and amount of surfactant is essential to improve the thermodynamic stability and transparency of NEs. The toxicity of the constituents is a major concern of NE-based systems. Topically applied surfactants in high concentrations can cause skin irritation. As a result, it is very important to choose the appropriate concentration of Smix, which can be the lowest in the mixture[40,41]. When the drug was added to the formulation, there was no noticeable change in the phase behavior while reading the pseudo-ternary phase diagram. This can be explained by the stability and production of NE, which consists of nonionic surfactants that are not affected by changes in pH or ionic strength[42]. Therefore, the optimized formulation was selected based on the lowest Smix concentration among the transparent formulations obtained using the pseudo-ternary phase diagram

Table 3 — Thermodynamic stability test of optimized formulation selected from pseudo ternary phase diagram.

Smix	Percentage (w/w) of components			Thermodynamic stability studies		
Tween 80:PEG 400	Oil	Smix	Water	Heating- cooling	Freeze-thaw	Centrifugation
4:1	0.47	4.29	95.24	✓	✓	✓

✓=Passes the test as no significant change is observed

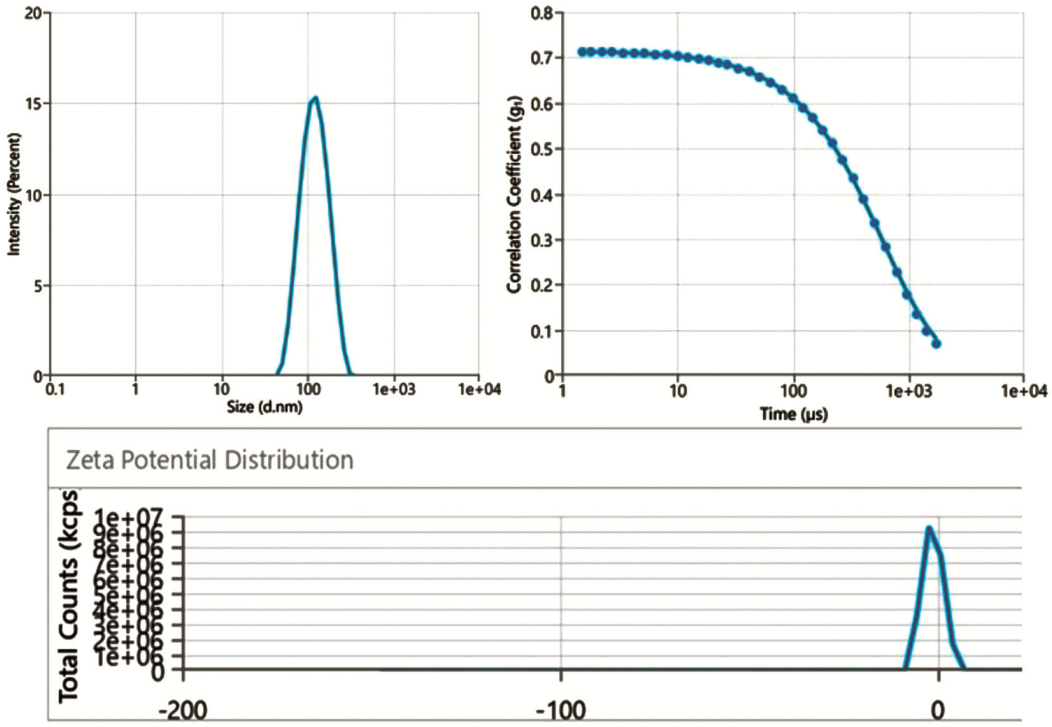

Fig 4 — Micrograph showing (a) droplet size and PDI value; (b) Zeta Potential of the clove oil based itraconazole loaded o/w type nanoemulsion batch

and it was further evaluated for thermodynamic stability studies.

3.5 Thermodynamic stability studies

To solve the problem of metastable formation, thermodynamic stability tests were carried out. As shown in Table 3, the selected formulations underwent various stress tests including centrifugation, heating-cooling cycle and freeze-thaw cycle. The selected NE underwent further characterization including droplet size, PDI and viscosity measurement. The parameters were found to remain unchanged reflecting a stable formulation[43].

3.6 Zeta Potential, PDI, and droplet size measurement

Both the droplet size and the PDI of NE are important for predicting the *in vivo* physical stability of nanoemulsion. The small droplet size prevents any flocculation, allowing the system to remain dispersed without segregation. In compliance with the earlier reports, the correlation function has been observed to decrease with time which elucidates the duration a particle remains in a particular position within the sample. Initially, the correlation function exhibits linearity and near constancy, signifying the particle's continued presence at its preceding location. Subsequently, decline in the correlation function indicates particle movement. Swift movement of small particles results in a rapid decay, while larger particles, moving more slowly, lead to a delayed decay in the correlation function[44]. The droplet size and PDI of the optimized formulation were found to be 107.84 ± 2.76 nm and 0.16±0.08, respectively as shown in Fig. 4(a). A zeta potential micrograph of optimized NE is shown in Fig. 4(b), the zeta potential was observed to be -0.85± 0.32 mV (Table 4). A low PDI value indicates greater uniformity of formulations[45]. All values were in the optimal range, showing stable NE with appropriate size distribution[46]. However, some modifications may also be executed for better zeta potential values.

Table 4 — Summary of the observed values obtained after checking the Droplet size, PDI, Zeta Potential and viscosity of the clove oil based itraconazole loaded nanoemulsion formulation.

Nanoemulsion characterization parameter	Value observed
Droplet size	107.84 ± 2.76 nm
PDI	0.16 ± 0.08
Zeta Potential	- 0.85 ± 0.32 mV
Viscosity	24 ± 2.34 cP

3.7 Viscosity Measurement

For a stable NE, one of the important parameters is the viscosity of formulation for topical delivery of drugs. Higher viscosity provides increased residence time in the formulation. Optimal viscosity offers smooth topical application and better retention of formulation at the site of application[47]. The high viscosity of PEG 400 can support NE to adhere to the skin, while the liquid form of NE offers better spread ability to the skin. Overall, a very low viscosity of 25 ± 2.34 cP was observed, which is expected for NE as shown in Table 4. So, it will be wiser attempt to further convert this NE it into gel form, called nanoemulgel to provide better mucoadhesion and contact time.

4 Conclusion

Based on the research, it can be inferred that the construction of pseudo ternary phase diagrams using the water titration method could be a useful tool for designing a NE that determines the ideal ratios of oil, Smix, and water content in order to produce an emulsion that is transparent and thermodynamically stable. When compared to single surfactant systems, mixed surfactant systems performed better in producing bigger monophasic zones. The foundation for calculating and creating pseudo-ternary phase diagrams was elucidated in this study. By choosing formulations based on phase diagrams, metastable formulations can be avoided with the lowest surfactant concentration in the shortest amount of time. For the chosen NE, consideration has also been given to thermodynamic stability and its function. The fact that droplet size, and PDI were all within optimal range indicates that the chosen formulation had the right size distribution. To attain the lowest globule size, narrowest size distribution, and highest zeta potential value, the systematic design of the experiment (DoE) tool can be used for further optimization. This approach can be applied to comprehend and evaluate the structural formation during the production of a particularly stable NE intended for topical administration. The formulation will be converted to a nanoemulgel for improved topical delivery by extending the formulation's contact time on the application site. In future, various parameters, including surface morphology, in vitro release, drug content, skin penetration, irritation studies, free energy calculations etc. will be further assessed for the developed formulation.

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