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Formulation And Evaluation of Microemulsion Based Itraconazole Gel

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ABSTRACT

Background:The microemulsion is one of the most promising sub-micron carriers for topical drug administration because it has benefits including high drug-loading capacity and good skin penetration. Topical fungal infections may be effectively treated with Itraconazole (a broad- spectrum antifungal drug) gel produced from microemulsions. **Objective**: The objective of the research is to formulate and evaluate a Microemulgel system loaded with the drug Itraconazole microemulsion for effective treatment of skin infections. **Methods**: Optimized microemulsion batches were selected through a pseudo-ternary phase diagram (using IPM, tween 80, and PEG 400 as oil, surfactant, and co-surfactant, respectively), followed by stability studies and characterization. As a gelling agent, xanthan gum is used. The characteristics and stability of an itraconazole microemulsion-based gel were studied, and in vitro drug diffusion of the optimized MEG was conducted. **Results**: Isopropyl myristate was used as the oil, tween 80 as the surfactant, and PEG 400 as the co- surfactant to produce the microemulsion. With a Smix ratio of 3:1, the largest clear microemulsion zone was identified. The drug content, Viscosity, and zone of inhibition were found to be in the desired range. It was found that the droplet size of optimized formulations was within the desired range (<200nm). The prepared microemulgel was discovered to have good spreadability and texture (from selected microemulsion batches). and it was found that the optimized MEG 3 had a 94.12% in vitro drug diffusion rate. When compared to the microemulsion (ME2) and the conventional gel, the drug from MEG3 Gel showed far better in vitro antifungal studies. Like this, it was discovered that MEG 3 Gel's zone of inhibition (against Candida albicans) had a larger diameter than the microemulsion batch (ME 2). Moreover. Furthermore, according to the stability investigations, the formulation was stable across a range of temperatures. **Conclusion:** Itraconazole-loaded microemulsion-based gel could be used effectively for the treatment of topical fungal infections.

Keywords: Microemulsion: Pseudo ternary phase diagram: Candida albicans: Cosurfactant: Microemulgel.

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1.Introduction

The frequency of obtaining bacterial, viral, or fungal infections diseases increases each year due to the ease of transmission from person to person. Also, Fungal infection is a common infection that affects two-thirds of the population in the world [1]. Recently, there have been more and more cases of fungal infections caused by fungi such as those from the genera Candida, Aspergillus, and Cryptococcus. Although candida skin infections can happen practically anywhere on the body, they are most frequently seen in intertriginous areas, or places where two areas of skin might rub or touch one another [2].

Many antifungal drugs are available for the treatment of fungal infections like Itraconazole, Miconazole, Ketoconazole, etc. Itraconazole is a triazole antifungal agent, compared with other antifungal agents, ITZ shows lower toxicity. With the wide range of action. Infections caused by fungi are treated with ITZ. It belongs to BCS class-II drugs i.e. lower solubility with 55% oral bioavailability. ITZ is a weak base with a pKa 3.7 and relatively insoluble in water (S<1 µg/ml). It has extremely low aqueous solubility and poor dissolution rate in the gastrointestinal tract so its oral administration is faced with large interindividual variations in bioavailability. It is having certain oral side effects like nausea, vomiting, dizziness, stomach upset, trouble breathing, swelling feet, hair loss, irregular heartbeat, hearing loss, etc. upon recurrent prolonged use. Log P is high which indicates high permeability through the membrane and it is beneficial for topical delivery. It has been used successfully in the treatment and prevention of Candida albicans infections [3].

Topical treatments, such as creams and ointments, are sticky and need rubbing, which can make patients uncomfortable. Gels are characterized as a semi-rigid system in which the dispersion medium's moment is limited by interlacing three-dimensional networks of particles. They are non-invasive and patient-friendly, are less greasy, and can be easily removed from the skin. They're also affordable, have a localized action with little side effects, boost medicine absorption, reduce dose frequency, and stabilize drug distribution patterns. Despite the many benefits of gels, one important drawback is the delivery of hydrophobic medicines [4].

Microemulsions (MEs) have gained in popularity and attention in recent years due to their unique properties. The stable MEs are simple to make and can improve the solubilizing efficacy of both hydrophilic and lipophilic pharmaceuticals, hence increasing drug permeability 5. ME's low viscosity, on the other hand, makes it difficult to apply to the skin and reduces patient compliance. When compared to solution, gel, or formulations, MEs or ME gels dramatically improve medication absorption. Natural polymers are cost-effective in distribution systems because they are readily available [6].

Xanthan gum in the preparation of ME gels, natural polymers, to develop the viscosity properties and drug release of the produced gels. As a result, it helps to solubilize the lipophilic drug moiety and it shows rapid and efficient penetration to the skin. So, it is beneficial for the topical drug.

2.Materials and Methods

Itraconazole was obtained as a gift sample from Dhamtec Pharm, Mumbai. Isopropyl myristate (IPM) oil, oleic acid, and Caster Oil, Tween 20, Tween 80, Tween 40, propylene glycol, PEG 400, and PEG 200 were purchased from Research Lab, Fine Chem Industries, (Mumbai, India). Xanthan gum was purchased from Arihant Innochem Pvt.Ltd and Double distilled water was used

throughout the study. In addition, only analytical-grade chemical reagents and solvents were being used.

UV- visible Spectrophotometry

Making an itraconazole stock solution (in methanol and PBS 5.5). Weighed and placed into a 100 mL volumetric flask was 10 milligrammes of itraconazole. It was dissolved and diluted with solvent to the desired strength to create a stock solution containing 100g/mL. The drug's lambda max was determined using spectrometric scanning. 1 mL of the stock solution was pipetted out, diluted with methanol to 10 mL, then scanned between 200 and 400 nm in wavelength. Pipetting 0.2, 0.4, 0.6, 0.8, and 0.1 mL of the stock solution and dilution with up to 10 mL of methanol were used to create a series of dilutions for the calibration curve of itraconazole to be plotted from the stock solution, resulting in 2, 4, 6, 8, and 10 ppm solutions, respectively. Using a UV-visible spectrophotometer, absorbance was measured at 262 nm and 266 nm. To ensure linearity, this experiment was run in triplicate, and a calibration curve was drawn.

FTIR Spectroscopy

The FTIR spectrum of pure drug and excipients along with the mixture of drug and excipients, were recorded by FTIR, and compatibility of drug and excipients was checked by comparing the spectra.

Solubility Study of ITZ [7.8]

Oils and excipients were selected on the criteria of highest solubility of ITZ in them. The various components of microemulsion such as oils (IPM, oleic acid, IPM: oleic acid (1:1), castor oil), surfactants (Tween 80 and Tween 40, Tween 20), and co-surfactants (Propylene glycol 200, propylene glycol, Propylene glycol 400) were selected to perform solubility studies of Itraconazole. The drug was over-added to the solvents in tightly covered vials and stored at 37°C under agitation in the water bath shaker for 72 hours to allow for equilibration. The dispersions were centrifuged at 3000 rpm for 15 min and the supernatant was filtered through the membrane filter. The amount of ITZ solubilized was analyzed using UV–visible spectrophotometer at 262 nm.

Construction of Pseudo ternary Phase Diagram

Using Chemix ternary diagram software, a pseudo ternary phase diagram was developed using a water titration method at room temperature (25°C). The surfactant and cosurfactant, Smix (km) mixed in the different weight ratios 1:1,1:2,1:3,2:1,2:3,3:1and 3:2. The oil to Smix ratio for each phase diagram was 1:9 or 2:8, 3:7,4:6,5:5,6:4,7:3,8:2,9:1 (%w/w). Each oil-mix combination is added a small amount of water at a time while the mixture is vigorously stirred to determine the microemulsion zone and until the mixture reaches a particular point where it becomes clear. To construct the pseudo-ternary phase diagram, the component concentrations were determined. Based on the results, the proper weight ratios of oil, surfactant, co-surfactant, and water were selected for the mixture's contents. Afterward, a phase diagram based on the readings was produced. Afterward, a phase diagram based on the readings was produced. The resulting phase diagram makes it possible to distinguish between the zones of coarse and microemulsion [9].

Preparation of ITZ ME

For the preparation of ME, a Smix ratio with the largest ME area was chosen. ITZ was dissolved in the mixture of oil and Smix to create seven different batches from this area. Using a magnetic stirrer (Remi, India), the prepared mixtures were combined at room temperature. Then, until a clear and transparent Microemulsion had been

obtained, double-distilled water was added drop by drop to this oil phase or mixture. Using a magnetic stirrer, the mixture was gently stirred for 15 to 20 minutes to help it stabilize and reach equilibrium. Then, all MEs carrying ITZ were kept at room temperature for storage. The formulation table is shown in Table 1: Formulation table of microemulsion from the pseudo ternary diagram [10].

4. Characterization of Microemulsion

Thermodynamic Stability

Thermodynamic stability of the prepared microemulsions at different concentrations of Oil mixture and Smix was performed to overcome the problem of metastable formulations. Initial screening of microemulsions was performed based on thermodynamic stability.

Heating Cooling Cycle

It was performed by keeping the microemulsions at two different temperatures i.e., refrigerated temperature (4°C) and at the higher temperature (45°C). Studying six cycles with storage at each temperature for at least 48 hours. Those formulations, which were stable at these temperatures, were subjected to further analysis.

Centrifugation

Those formulations that passed the heating cooling cycle were then subjected to a centrifugation test. The microemulsions were centrifuged at 3500 rpm for 30 minutes. The freeze-thaw stress test was conducted on the formulations that did not exhibit any phase separation.

Freeze Thaw Cycle

The microemulsions conducted three freeze-thaw cycles between -21°C and +25°C with storage at each temperature for at least 48 hours. This test was performed to see whether the microemulsions were stable at very low temperatures and whether it comes back to a stable form after freezing it.

Drug Entrapment Efficacy

The centrifuged method was used to estimate the amount of drug contained in the microemulsion.2 ml microemulsion was centrifuged for 20 min at 5000 rpm in a centrifuge tube and the supernatant was collected and proper dilution are prepared and scanned in UV visible spectrophotometer at 262 nm and the future calculated.

Globule Size and Polydispersity Index (PDI)

The average globule size and PDI of microemulsions were determined by photon correlation spectroscopy. Measurements were made using Zetasizer (Malvern Instruments), wherein light scattering was monitored at 25 oC at a 90o angle [12].

Measurement of Zeta Potential

The average zeta potential of the optimized microemulsions was measured using a Malvern Zeta seizer instrument at a temperature of 25 °C [13].

Transmission Electron Microscopy (TEM) Study

Using transmission electron microscopy (TEM), the morphology and structure of the microemulsion were examine [14].

Dilutability

To see if the system exhibits any sign of separation, the produced microemulsions were diluted with double distilled water in ratios of 1:10 and 1:100.

5. Formulation Microemulsion Based Gel

Using a dispersion method, the prepared and optimized ITZ microemulsion was incorporated into a hydrogel to form an Itraconazole Microemulgel. Xanthan gum was used in the preparation of the hydrogel. weighed xanthan gum and dispersed it in water with stirring and then the mixture was kept for swelling.Triethanolamine was added to the prepared gel to neutralize it, and

it was then mixed once more to achieve transparency glycerine was added as necessary for gel consistency and methyl and propyl parabens are added as preservatives.The formulation table is shown in Table 2: Formulation of Microemulgel containing ITZ Microemulsion [15].

6. Evaluation of Microemulsion Based Gel

Homogeneity and Grittiness

The homogeneity of all the formulated gels was checked visually for the presence of any aggregates or clumps.

pH Measurement

The pH of each gel was measured, using a pH meter, which was calibrated before use with standard buffer solutions at pH 4 and 7.

Determination of Viscosity

The main criterion for evaluating the topical dose form is viscosity. As a result, the viscosities of formulations were measured using a Brookfield viscometer fixed at 37°C with a Spindle number of S-63 [16].

Spreadability

Using two glass slides that were each 7.5 cm long, spreadability was tested. On a single glass slide, 350 mg of Microemulgel was accurately measured out. It was positioned with another glass slide positioned 5 cm above it. Following one minute, the diameter of the circle that had been spread in cm was recorded. A weight of 5 grams was kept on the upper slide. The sort of gel is shown by the diameter that was detected [17].

Extrudability Determination

The extrudability test was chosen to investigate how much force or pressure is necessary for pushing material out of tubes. By applying weights, the gel was forced out of an aluminum collapsible tube, and the area was measured for calculation. 1 gm of drug-incorporated gel was withdrawn and dissolved in a beaker containing PBS of 5.5. The solution was filtered and necessary dilutions were made. The drug content was determined by using a UV-Vis spectrophotometer (Shimadzu 1800) at 262 nm.

In-vitro Drug Diffusion Release Study

An *in-vitro* diffusion study of microemulsion gels was carried out by using a set of Franz diffusion cells, to study the release rate of drug from formulation. To investigate the rate at which a drug is released from its formulation, a set of Franz diffusion cells was used in an *in- vitro* diffusion investigation of microemulsion gels. The receptor medium was poured into the receptor chamber (PBS pH 5.5). Throughout the experiment, the temperature of the receptor media was maintained at 37°C ± 1°C by running water through a jacket that encloses the cell body. A dialysis membrane was clamped between two chambers after it had already been soaked in receptor media for 12 hours. The donor cell was given 1g of the formulation. After a specific amount of time, 1 ml samples were then taken from the receptor cell. After each collection, an equal amount of new medium was added to maintain the volume. The withdrawn samples were submitted to spectrophotometric analysis using fresh receptor media as the blank, diluting them as necessary. An equation created from standard calibration was used to calculate the drug concentration delivered at a specific time interval [19].

In-vitro Antifungal Activity

In- vitro antifungal studies were performed against Candida Albicans and Sabouraud's agar medium by the agar-cup method. Suspension of C. albicans was inoculated in Sabouraud dextrose broth and then poured into a sterile Petri dish and allowed to solidify. Using an borer, wells were made on the plate, and prepared formulations containing 1% ITZ, Microemulsion,

Microemulgel and Marketed formulation were added to each well. After that plates were incubated at 37°C±1°C for 24 h. The zone of inhibition of ITZ released from prepared microemulsion and microemulgel, marketed formulation was calculated in centimeters by the formulation was measured after 24 h at 30°C [20,21].

Stability Studies

Stability tests on the optimized microemulsion-based gel formulations were conducted over three months at various temperatures. Formulations were kept at It was carried out at 25°C ± 2°C/ 60% RH ± 5% RH and 40°C ± 2°C/ 75% RH ± 5% RH. All the formulations were tested for spreadability, color, grittiness, pH, and drug content after one month, two months, and three months.

7. Results and Discussion

7.1 Ultraviolet-Visible (UV-Vis) Spectrophotometry

The peak in the UV-Vis spectrum analysis of Itraconazole, was observed at 262 nm in methanol and 266 nm in PBS pH 5.5. (Figure 1) and (Figure 3) The concentration from 2 to 10 ppm of ITZ in methanol was selected for the calibration curve (Figure 2) shows the calibration curve of the ITZ. The R2 was found to be 0.9994, indicating that linearity.

The value of R2 was found to be 0.9978 Indicating the relation between drug concentration and absorbance was linear in the selected range. The absorbance of different concentrations of the drug in phosphate buffer solution pH5.5(Figure 4) shows the calibration curve and linearity of ITZ in PBS 5.5.

7.2 Drug excipient compatibility studies by FTIR analysis

In the figure, FTIR of the drug shows the characteristic peaks at 3379.2cm–1attributes to N-H Amide, C-O stretching observed at 1273.03 cm–1, at 732.9 cm–1 C-Cl stretching was observed while CN alkyl amine stretching was observed at 1188 cm-1. These characteristics peaks observed give conformation and purity of the drug. (Figure 5).

In the figure, FTIR of the drug and excipients was studied for compatibility studies it shows the peaks at 732 cm–1 showing the C-Cl stretching, the peak observed at 1679 cm–1 shows the CO stretching, NH amide stretching observed at 3379 cm-1 and peak observed at 1249 cm-1 shows the characteristic peak of C-O-C stretching. Carbonyl group stretching was observed at 1200- 970 cm-1. These observed peaks are found to resemble the peaks observed in the FTIR of the drug which shows that there were no interactions between the Itraconazole and excipients. Hence it states that the drug and excipients are compatible with each other (Figure 6).

7.3 Solubility Study of Itraconazole

ITZ solubility in various oils, surfactants, and cosurfactants was determined to screen the constituents for the formation of microemulsions containing ITZ. Solubility of ITZ was highest in IPM (60.21±1.76mg/ml) among the Two oils, followed by alone oleic acid alone (45.6±2.12 mg/ml); while in olive oil, ITZ has the lowest solubility (26.78±2.94 mg/ml). IPM was selected for further study owing to its solubility profile.

The solubility of ITZ was higher in Tween 80 (14.69±2.94mg/ml), followed by Tween 40, Tween 20 (7.36±1.47 mg/ml), and (4.82±0.45 mg/ml), among surfactants. However, the results of compatibility studies showed that Tween 80 was compatible with the selected oil phase in all proportions. PEG 400 demonstrated higher solubility of ITZ (7.98±3.30 mg/ml) among the two co-surfactants followed by alone PEG 200 alone (3.87±0.07mg/ml); while in Propylene glycol, ITZ has the lowest solubility

(2.5±0.08mg/ml). among the tested co-surfactants; hence it was selected for further study. The blends of a mixed system of selected oil phase (IPM) and surfactant (Tween 80) with co-surfactant (Propylene glycol 400) showed miscibility and transparency in all proportions. (Figure 7).

7.4 Preparation of Ternary Phase Diagram

The zone of the clear microemulsion was determined using a pseudo-ternary phase diagram. Pseudo-ternary phase diagrams were created for microemulsions with various Smix ratios to determine the appropriate components and their concentration ranges. It was possible to identify regions of microemulsions and improve microemulsion formulations. In Figure 3, the remaining area represents turbid microemulsion whereas the shaded area represents transparent or clear microemulsion. A smix ratio of 3:1 was determined to produce the largest transparent microemulsion region, hence that region was chosen to produce the ideal microemulsion. (Figure 8).

7.5 Evaluation Parameters of Microemulsion:

Thermodynamic stability of Microemulsion batches

From the test, it is found to be that ME2 and ME6 were stable batches as compared to other batches of microemulsion like ME1, ME3, ME4, ME5, ME7 since appearance and shows separation of phase during storage. Therefore, the ME2 and ME6 were subjected to thermodynamic stability studies. The thermodynamic stability of batches ME2 and ME6 was performed to ensure their stability under various temperatures. ME2 was found to be a more stable batch as it passed all the conditions of Heating cooling cycles, Centrifugation, and freeze thaw cycle and shows no phase separation (Table 4). According to this observation, batch ME2 was more stable than batch ME6.

Entrapment efficiency and Physical appearance of ME after 24 hours

The pseudo ternary phase diagram indicates that the batch was formed, and the entrapment efficiency of formulated batches indicates that the percentage of entrapment is approximately 73.82% to 91.73%. Batches ME2 and ME6 showed the highest levels of entrapment; they also displayed a clear appearance after 24 hours of preparation, while other batches lacked transparency for further study selection (Table 3). After being stored for a few days, it was discovered that some of the batch was phase separated, therefore ME2 and ME6 were chosen for further investigation.

Globule size & PDI

The average particle size of the optimized batch was found to be 98.80 nm and shows homogenous as its poly-dispersibility index was found to be 0.191 (Figure 9). Also, reports suggest that the oil concentration affects the globule size, more the concentration of oil higher will be the globule size.

Zeta Potential

The zeta potential result of the optimized formulation showed a value of -29.8 mV (Figure 10). Reports indicate that the value above or below ± 30 mV indicates highly stable microemulsion formulation.

Transmission Electron Microscopy

TEM analysis of the optimized batch it shows that the morphology of the globules was spherical and much more particles were found to be below 98.80 nm. TEM study confirms that the prepared microemulsion having desired particle size and no agglomeration of particles found between them which states that microemulsion is the stable form (Figure 11).

Dilutability

The prepared optimized batch of microemulsion ME2, diluted with distilled water in 1:100 ratio and visually checked for phase separation and clarity. There is no phase separation occurred, therefore it is confirmed that it is an oil in water microemulsion

7.6 Evaluation of Prepared Microemulgel

Homogeneity and Grittiness

All the prepared formulations of microemulgels showed good homogeneity without any particulate matter observation, free from grittiness (Table 5).

Determination of pH

pH of all the formulated microemulgels was found to be in the range of 5.8 to 6.0. Hence all microemulgels have an acceptable pH range (Table 5).

Determination of Viscosity

The measurements of the viscosity of the prepared microemulgels were carried out MEG3 shows high viscosity as compared to other gels (Table 5). This study demonstrates that the viscosity increases with an increase in the concentration of Xanthan Gum (gelling agent) and it also affects the release of the drug in the In-vitro studies.

Determination of Spreadability

The spreadability of formulated gel is calculated and found in the range of 18.21 to 20.71 (Table 5). This clearly states that the MEG3 is having less spreadability effect while covering less area and might show a targeted effect.

Determination of Extrudability

Extrudability of the MEG3 shows maximum extrudation of gel when the force is applied while MEG1 and MEG2 have less extrudation (Table 5).

% Drug content

MEG3 shows a high % drug content in comparison with MEG1 and MEG2. % Drug content of the gel does not vary much and it founds between 85.12% to 94.12% (Table 5).

7.6 In-vitro Diffusion Study

The *In-vitro* release study of prepared microemulgel formulation was determined by Franze diffusion cell apparatus. The drug release was carried out for 8 hrs in 5.5 phosphate buffer. The

% of drug release is found to be in the order of MEG3 > MEG2 > MEG1. Thus MEG3 shows the highest release while all the formulation shows controlled release (Figure 12).

7.7 Drug Release Kinetics study

Microemulgel kinetic models such as the Higuchi model, Higuchi model of zero order, and the Hixson model of first order are used to determine the drug release mechanism. Since they had the highest R2 values, the zero-order release kinetic model fit all of the formulations the best, according to the R2 values for each formulation (Table 6). Due to the highest R2 values, it can be concluded from the above table that MEG3 was the ideal microemulgel formulation.

7.8 In- vitro Antifungal Study

Antifungal studies carried out on the Candida albicans and zone of inhibition of Pure drug, Microemulsion, marketed gel, and optimized microemulgel are compared and the result states that the microemulgel shows much more promising result as compared to the marketed gel and microemulsion (Figure 13), (Table 7).

7.9 Stability Study

The stability study of the Microemulsion based gels was performed as per ICH guidelines. Freshly prepared formulations were divided into groups and kept at specified storage conditions as per ICH guidelines. Samples were withdrawn periodically and tested for various evaluation parameters. The results of the stability study are tabulated in (Table 8). The stability study of the

Microemulgel of MEG3 revealed no changes in its homogeneity, clarity, pH, texture, viscosity, spreadability, extrudability, or drug content since the formulation maintained all its properties when stored at the recommended temperatures.

8. Conclusion

In the present study, the application of microemulsion systems in the gel form for the topical delivery of voriconazole was studied. The pseudo ternary phase was used to optimize the formulations and selected formulations were evaluated. ME gel produced with oil (IPM), S/Cos (Tween 80: PEG 400), water, and (Xanthan gum) outperformed all other formulations in terms of overall formulation quality. Itraconazole is made available in formulations by the developed microemulsion system, which also allows for the solubilization of hydrophobic drugs. The developed microemulsion system's globule size and zeta potential were 98.80 dnm and -29.8 respectively, confirming the stability and proper formulation of the microemulsion. The prepared ME gel can be considered a cost-effective formulation because of the reduction of the topical dose of itraconazole in the formulation. The ME2 batch is an optimized formulation. The prepared microemulsion gel shows a better release profile than the marketed preparation. The results of in vitro antifungal activity of Itraconazole against candida albicans inferred that the microemulsion based gel is more efficacious in contrast to microemulsion and conventional gel. Furthermore, the formulations were found to be non-irritant. Hence, the prepared formulation (microemulsion-based gel) could be used for the treatment of cutaneous fungal infections effectively. So itraconazole ME gel can be used as an anti-fungal agent for topical drug delivery.

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Table 1: Formulation Table Of Microemulsion From The Pseudo Ternary Diagram

Batch code	Oil (IPM)	Smix (3:1) (Tween 80: PEG 400)	Water
ME1	10	50	40
ME2	10	60	30
ME3	10	70	20
ME4	20	40	40
ME5	20	50	30
ME6	20	60	20
ME7	30	40	30

Table 2: Formulation Of Microemulgel Containing ITZ Microemulsion

Sr.no	Ingredients	Formulations		
		MEG1	MEG2	MEG3
1.	Xanthan	1 %	1.5%	2%
2.	Microemulsion containing ITZ	1%	1%	1%
3.	Methyl paraben	0.02	0.02	0.02
4.	Propyl paraben	0.01	0.01	0.01
5.	Triethanolamine	1 ml	1ml	1ml
6.	Propylene glycol	10 ml	10 ml	10 ml
7.	Distilled water	q.s	q.s	q.s

Table 3: Optimization of prepared batches from phase diagram based on %EE and observation after 24 hours

Batch code	Observation after 24 hr	Entrapment Efficiency (%)
ME1	Hazy	84.65
ME2	Clear	91.73
ME3	Almost clear	78.40
ME4	Hazy	82.41
ME5	Hazy	87.18
ME6	Clear	90.31
ME7	Hazy	73.82

Table 4: Thermodynamic stability study of batches

Batch No	Centrifugation test	Heating Cooling Cycle	Freeze Thaw Cycle
ME1	✓	×	×
ME2	✓	✓	✓
ME3	✓	✓	×
ME4	×	×	×
ME5	✓	×	×
ME6	✓	✓	×
ME7	×	×	×

Table 5: Formulation Of Different Concentration Of Microemulgel And Their Evaluated Parameters

Formulati on	Homogenei ty	pH	Viscosity(cp s)	Spreadabilit y	Extrudabili ty	Drug content (%)
MEG1	+++	5.8 + 0.02	9,520 + 0.13	20.71+0.75	17.25+ 0.25	85.12
MEG2	+++	5.9+ 0.03	9,480 + 13.1	19.54 +0.21	15.37+ 2.58	90.10
MEG3	+++	5.8 +0.01	10,800 + 23.01	18.21 + 0.12	14.25+ 2.31	94.12

Table 6: R^2 Values Of Formulated Microemulgel

Formulation Code	Zero-order	First order	Higuchi	Hixon Crowell	Kors-Peppas
MEG1	0.995	0.9702	0.9215	0.9851	0.9403
MEG2	0.9956	0.9708	0.918	0.988	0.9651
MEG3	0.9962	0.9732	0.9036	0.9882	0.9672

Table 7: Zone of Inhibition of formulated microemulgel

Sr.no	Sample	Zone of Inhibition (mm)
1.	Itraconazole (drug)	25 mm
2.	Microemulsion	27 mm
3.	Microemulsion based gel	30 mm
4.	Marketed formulation	20 mm

Table 8: Stability study

Formulation	**MEG 3**			
Storage Condition	40℃ ± 2℃ / 75 % RH ± 5 % RH			
Time interval (months)	**Zero month**	**After one month**	**After two months**	**After three months**
Homogeneity	+++	+++	+++	+++
Grittiness	+++	+++	+++	+++
pH	5.8 ±0.01	5.8 ±0.01	5.8±0.05	5.8 ±0.01
Viscosity (cP)	10,800	10,800	10,850	10,860
Drug Content	94.12 %	94.01 %	93.45 %	93.40 %
*** n (number of observations) = 03**				
+++ Excellent, ++ Good, + Satisfactory, - Poor, -- Fail				

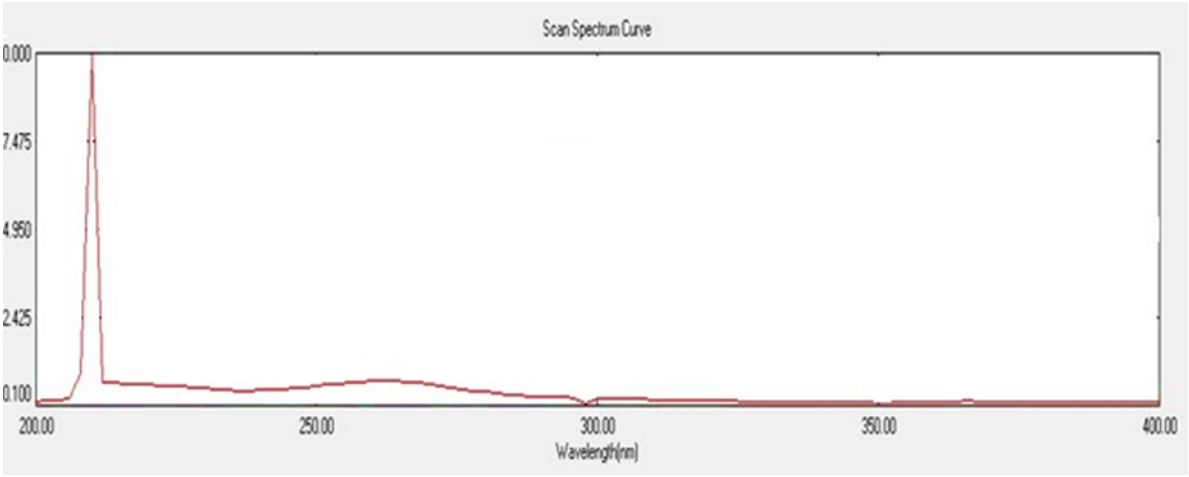

Fig 1: UV Spectra of Itraconazole In Methanol

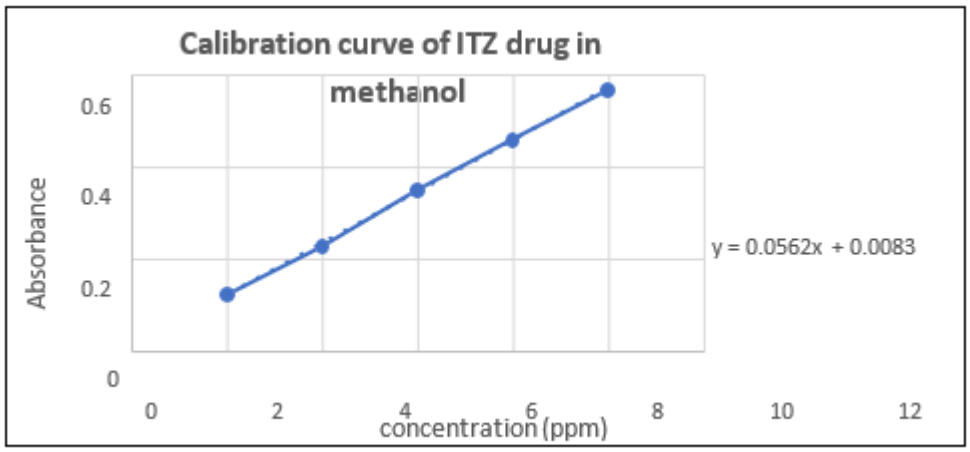

Fig 2: Calibration Curve Of Itraconazole In Methanol

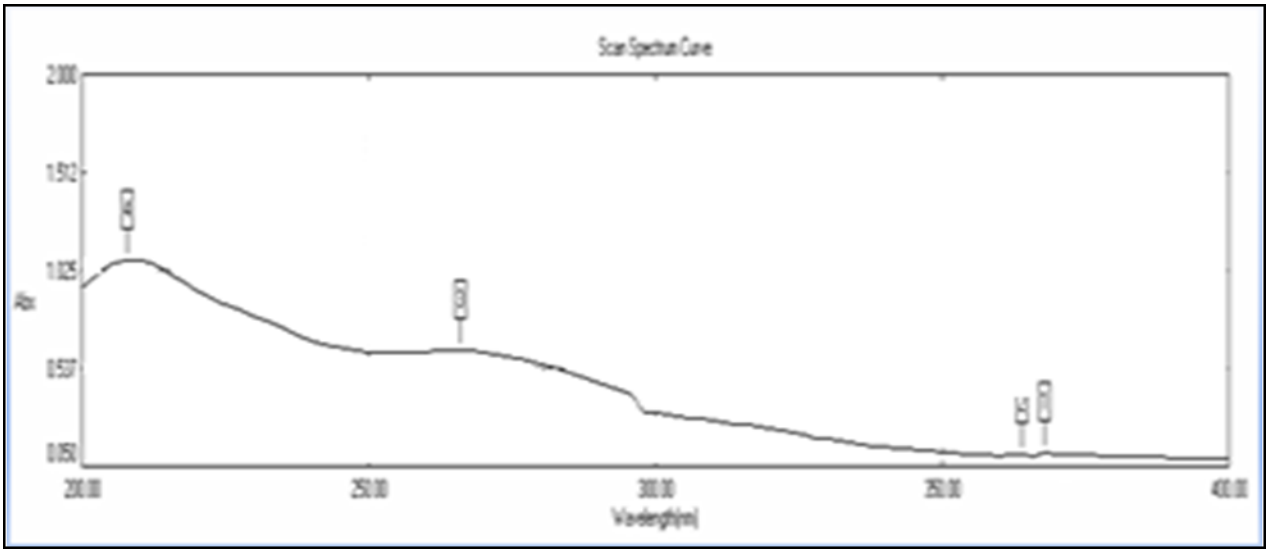

Fig 3: UV Spectra of Itraconazole in Phosphate buffer pH 5.5

A

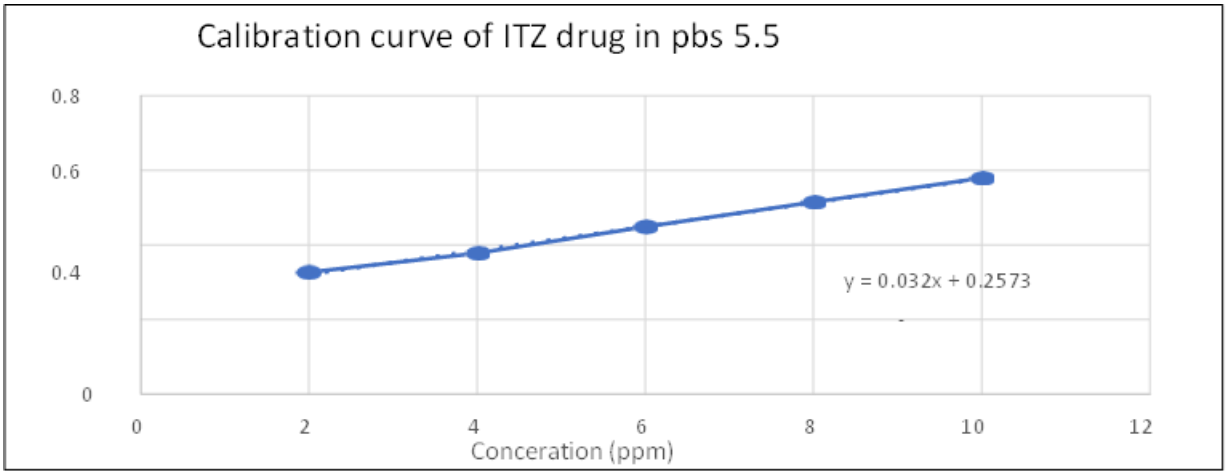

Fig 4: Calibration curve of Itraconazole in Phosphate buffer pH 5.5

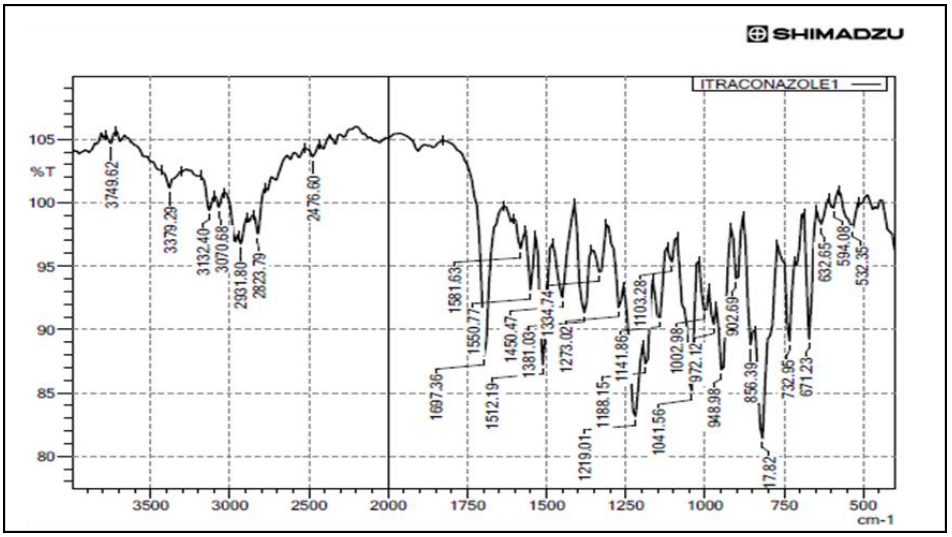

Fig 4: FTIR Spectra of Itraconazole drug

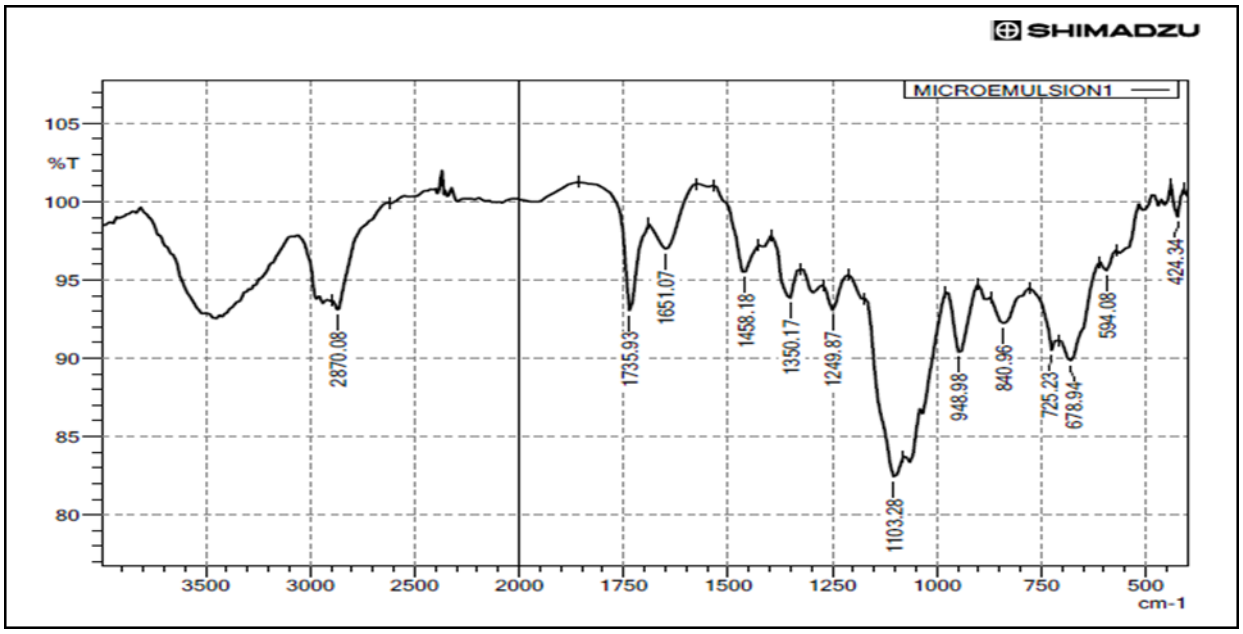

Fig 5: FTIR Spectra of Formulation Solubility Study of Itraconazole

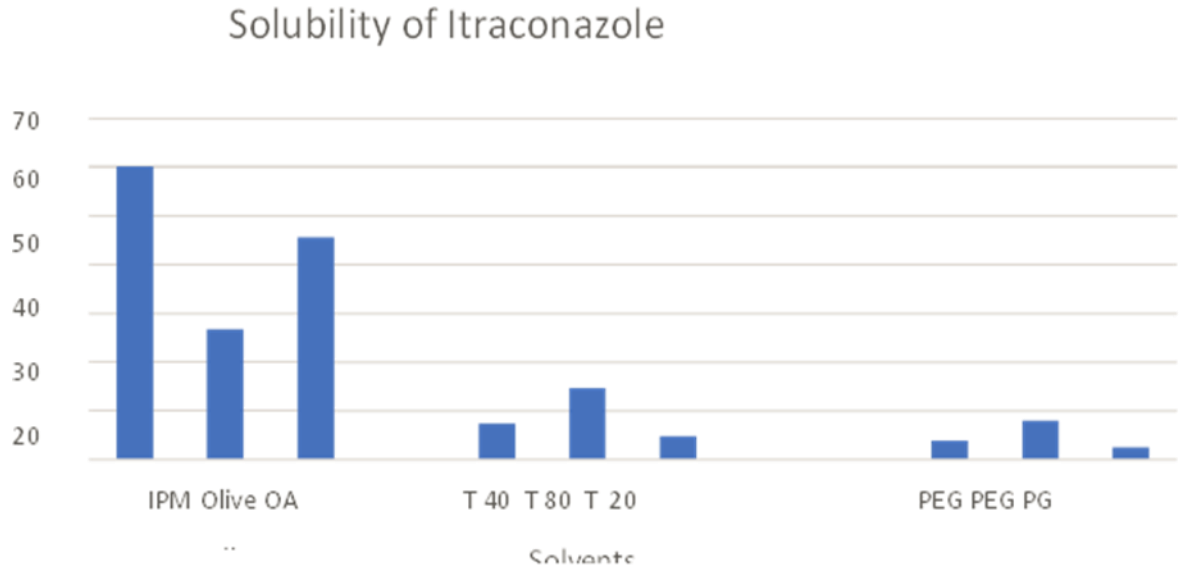

Fig 6: Graphical Representation of Solubility of ITZ

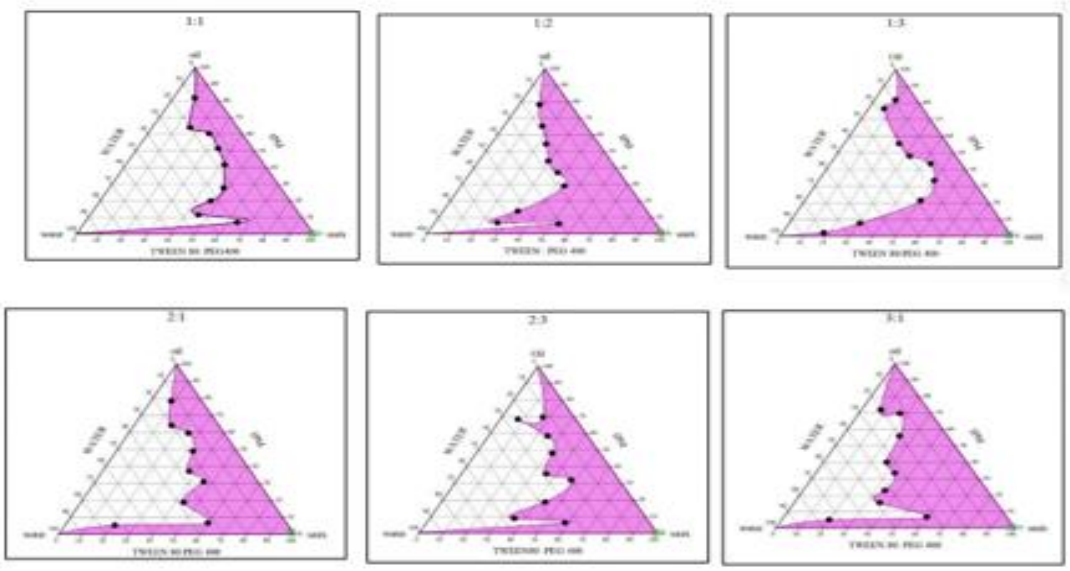

Fig 7: Pseudo Ternary Phase Diagram of Various Ratio Combination (1:1, 1:2,1:3, 2:1,2:3and 3:1) Containing Smix of Tween 80: PEG 400

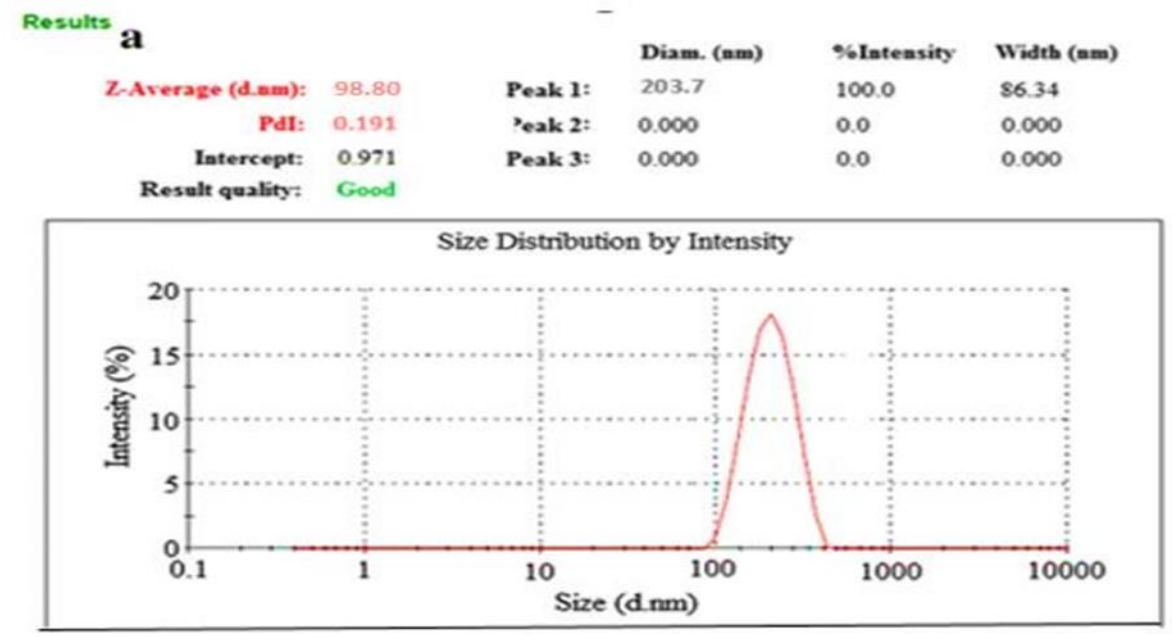

Fig 8: Globule Size and Poly-dispersity Index (PDI) of Optimized Microemulsion

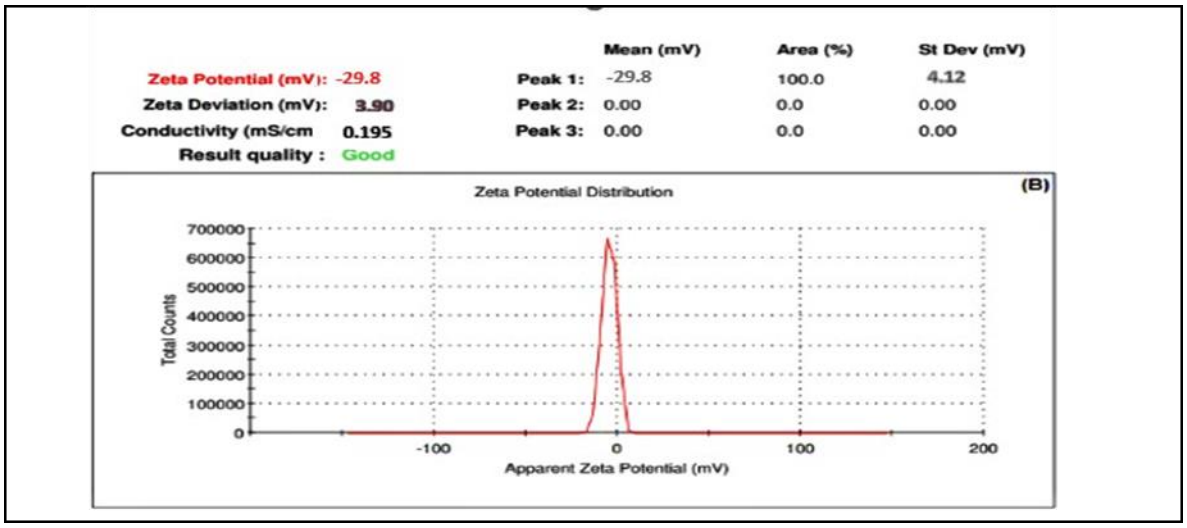

Fig 9: Zeta potential of Optimized Microemulsion

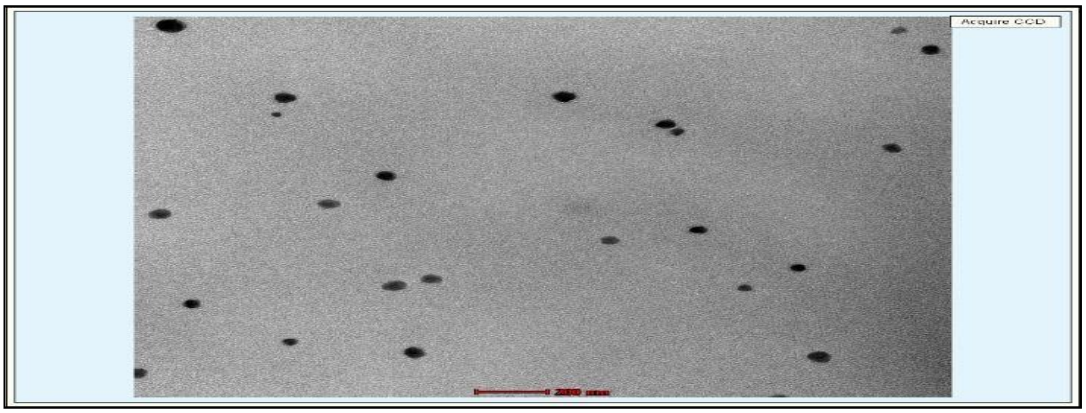

Fig No.10: TEM Image of Optimized Microemulsion

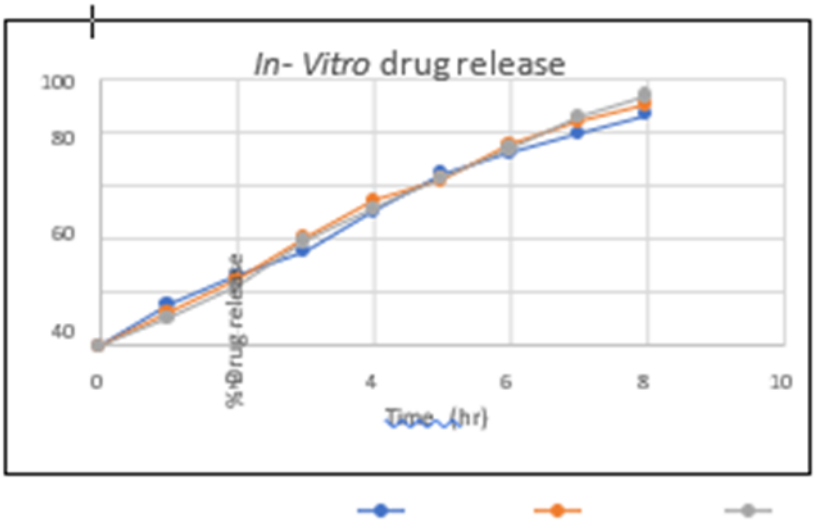

Fig No.11: *In-vitro* drug release of ITZ from Microemulgel

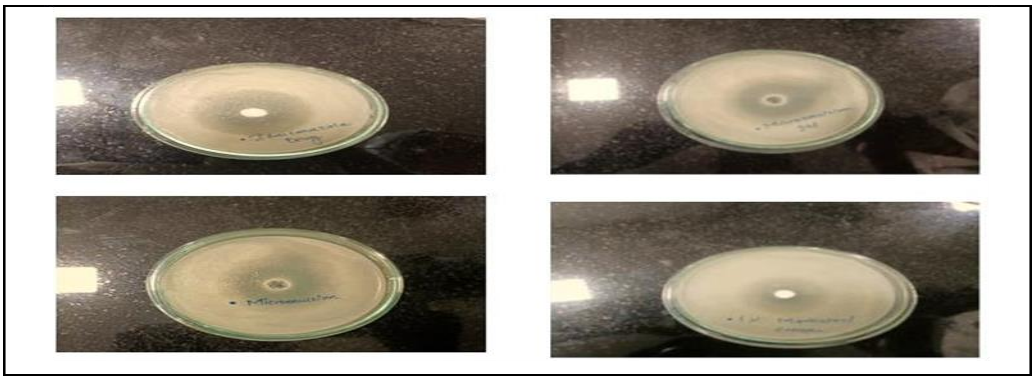

Fig 11: *In-Vitro* Antifungal Study of Drug, Microemulsion, Microemulgel, and Marketed Formulation