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FORMULATION AND EVALUATION OF ANTIFUNGAL MICROEMULSION BASED GEL FOR TOPICAL DRUG DELIVERY USING MILLETIA PINNATA

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ABSTRACT

The goal of this study was to develop and test a topical gel containing an Itraconazole microemulsion (ITZ). A preformulation research was conducted before the formulation of Itraconazole microemulsion. To determine the maximal solubility of ITZ in oils, surfactants and co-surfactants were tested to determine excipient potential. In order to microemulsion region, with Karanj oil as the oil phase, Tween 80 as the surfactant, and Isopropyl alcohol (IPA) as the co-surfactant, a pseudoternary phase diagram was created. The optimized ME of ITZ was characterized by its qualitative & Quantitative test & incorporated into polymeric gels of Carbopol (CBP), Xanthan gum, Carbopol 934, Carboxymethyl cellulose (CMC), Carboxymethyl -Tamrind gum (CMTG). ME evaluated by % transmittance, Viscosity, pH, particle size, zeta potential, Physical appearance, Drug content, pH, spreadability, viscosity, In -vitro release. Stable ME was obtained when Karanj oil was taken as oil phase, Tween 80 as surfactant & IPA as co-surfactant at the weight ratio of 5:45:50. The optimized ME based gel shows pH range 6.0- 6.34, Spreadability in the range of 0.56-1.06gm.cm/sec. The viscosity study indicated pseudoplastic behavior of all ME based gel formulations. Amongst the studied ME gels CBP: CMTG containing gels showed maximum drug release at the end of 6h. The prepared MEG show better release profile than marketed preparation.

KEYWORDS: Itraconazole, Microemulsion based gel, Pseudoternary Phase Diagram, Topical drug delivery.

INTRODUCTION

Approximately two-thirds of the world's population is infected with a common fungal illness.[1] Fungal infection is a frequent infection that affects two-thirds of the world's population. In recent years, the prevalence of fungal infections caused by fungi including Candida, Aspergillus, and Cryptococcus has increased. Skin diseases caused by fungi are known as mycoses. Candida skin infections can affect practically any part of the body, but they're most common in intertriginous areas, where two skin patches rub or touch.[2,3]

Itraconazole (ITZ) is a triazole antifungal with a wide range of activity. It's a medication from the BCS class II. Bioavailability of Itraconazole in conventional dose formulations was around 15-20%. It has a 6-hour biological half-life. Constipation, abdominal pain, headache, and, in rare cases, heart failure have all been reported as side effects of ITZ. The fact that ITZ is contraindicated in patients with renal and/or hepatic impairment is also a drawback.[4,5]

Topical treatments, such as creams and ointments, are sticky and need rubbing, which can make patients uncomfortable. As a result of their numerous advantages over other semisolid preparations, gels have gained prominence in both the pharmaceutical and cosmetic fields.[6] Gels are characterised 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 localised action with little side effects, boost medicine absorption, reduce dose frequency, and stabilise drug distribution patterns.[6,7] Despite the many benefits of gels, one important drawback is the delivery of hydrophobic medicines. As a result, a microemulsion-based approach is being employed to break through this barrier, allowing even a hydrophobic medicinal moiety to benefit from the special features of gel.[8]

Microemulsions (MEs) have gained in popularity and attention in recent years due to their unique properties. Industrial laboratories, as well as academic researchers and those working in the pharmaceutical industry, have shown an interest in these compounds, which has led to their use in a variety of administration methods. The stable MEs are simple to make and can improve the solubilizing efficacy of both hydrophilic and lipophilic pharmaceuticals, hence increasing drug permeability.[9] ME's low viscosity, on the other hand, makes it difficult to

apply to the skin and reduces patient compliance.[10] 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. They're also biodegradable, biocompatible, and easily accepted by regulatory bodies.[11]

Polymers including carbopol (CBP), hydroxypropyl methylcellulose (HPMC), carboxymethyl-tamrind gum (CMTG), carboxymethyl cellulose (CMC), and in the creation of ME gels, natural polymers such as xanthan gum (XG) have been characterized.[29,12-14]

Karanj oil, a non-edible semi-drying fixed oil derived from seeds of Pongamia pinnnata belonging to the Fabaceae family, is one of the natural.[9] According to the literature, Karanj oil is a therapeutic oil that is mostly used to treat itches, abscesses, and skin problems.[10] As a result, Karanj oil can be utilised as an oil phase in the formulation of microemulsion-gels for topical delivery of drugs that are weakly water soluble, potentially improving absorption and prolonging drug release.

As a result, it was proposed to develop and test ME including topical gels of CBP, XG, TG, CMTG, and CMC for better hydrophobic drug delivery. Further research was carried out to determine the viscosity and drug release of the produced gels. ITZ's gastrointestinal adverse effects may be mitigated by a recently developed ME-based gel.

2. MATERIALS AND METHODS

2.1 Materials

Aurochem Pharmaceuticals Pvt. Ltd., Palghar, provided ITZ. Loba chemie, Mumbai, provided Tween 80, isopropyl alcohol (IPA), olive oil, Tween 20, polyethylene glycol 400 (PEG400), and carboxymethyl cellulose (CMC). S.D Lab chemical centre in Mumbai provided xanthan gum and oleic acid. All additional chemicals were acquired from Loba Chemie in Mumbai and were of analytical quality.

Table 1. Formulation of microemulsion based gels.

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Gel									
Carbopol-934 (gm)	0.5	1.0	1.5	-	-	-	-	-	-
Xanthan gum (gm)	-	-	-	0.5	1.0	1.5	-	-	-
CBP:XG (1:1) (gm)	-	-	-	-	-	-	1.0	-	-
CBP:CMC (1:1) (gm)	-	-	-	-	-	-	-	1.0	-
CBP:CMTG (1:1) (gm)	-	-	-	-	-	-	-	-	1.0

Water (ml)	100	100	100	100	100	100	100	100	100
Microemulsion									
Itraconazole (gm)	2	2	2	2	2	2	2	2	2
Karanj oil (ml)	5.41	5.41	5.41	5.41	5.41	5.41	5.41	5.41	5.41
Tween-80:IPA (6:4) (ml)	45	45	45	45	45	45	45	45	45
Water (ml)	50	50	50	50	50	50	50	50	50
Methyl paraben (gm)	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Propyl paraben (gm)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01

2.2 Solubility study of ITZ

The oils and excipients were chosen due to itraconazole high solubility in them. Based on the literature analysis, Karanj oil was chosen as an efficient excipient for micro- emulsion formation.

The solubility of itraconazole in several oils (Karanj oil, Olive oil, Oleic acid) was studied to determine the best oil for usage as the oil phase in microemulsion. Itraconazole solubility in several surfactants (Tween-20 and Tween-80) and cosurfactants (Isopropyl alcohol, propylene glycol PEG-200, PEG-400) was also investigated. In stoppered vials (capacity 10mL), an excess amount of itraconazole was added to 3mL of the specified oil, surfactant, and cosurfactant, and then preliminary mixing was carried out over magnetic stirrer for a few minutes. These vials were then held at 37 ± 0.5^{0}C for 72 hours in a mechanical bath shaker. After that, the equilibrated samples were centrifuged (Remi) for 15 minutes at 3000 rpm. The supernatant was collected, membrane was filtered and spectrometric sample measurements at 262nm. determined solubility after proper dilution by methanol.Each experiment was carried out three times.[15]

2.3 Construction of pseudoternary phase diagram

The difference fraction of mixed surfactant was often used in the building of a phase diagram, and the surfactant and cosurfactant optimal ratio (Km) was estimated using the microemulsion area. Km was investigated using a simple pseudoternary phase diagram. The generation of microemulsions utilising a four-component system consisting of an oil phase, a non-ionic surfactant, a cosurfactant, and purified water was investigated using pseudoternary phase diagrams (aqueous phase).

Titration of homogeneous liquid mixes of water, surfactant, and cosurfactant with oil phase at ambient temperature yielded the pseudo ternary phase diagram. Surfactant and co-surfactant were combined in a 1:9 to 9:1 ratio. The nine samples were mixed consistently and

independently with water, and then the oil was added drop by drop to the mixture. Water content was set at 2.0 gm, and the total amount of surfactant and co-surfactant was also set at 2.0 gm. To allow for equilibration, samples were agitated by a vortex shaker during the titration. The combination was visually evaluated for transparency after the addition of an aliquot of oil, until the system became slightly hazy. The microemulsion window was discovered to exist as the area where clear and transparent formulations may be seen upon visual inspection. The water ratio was held constant, and the oil, surfactant, and cosurfactant formed the pseudoternary phase diagram.[16]

2.3 Construction of Ternary Phase Diagram

The best surfactant and cosurfactant weight ratio (Km) was chosen. The contents of mixed surfactant and oil in the mixtures varied from 9:1 to 1:9. A homogeneous oil surfactant–cosurfactant blend was created, where Km was fixed and the contents of mixed surfactant and oil in the mixtures varied from 9:1 to 1:9. The total amount was kept at 1.0 g. Drop by drop, purified water was added to each mixture. To allow for equilibration, samples were agitated with a magnetic stirrer during the titration. The combination was visually evaluated for clarity after an aliquot of water was added until the system became slightly cloudy.[17]

2.4 Preparation of ITZ ME

The Smix ratio with the largest microemulsion region was chosen. Oil and Smix were blended in various quantities. Itraconazole was dissolved in a mixture of oil and Smix at room temperature using magnetic stirring. Dropwise additions of double distilled water to the oily mixture were made until a clear and transparent microemulsion was formed. With mild magnetic stirring, the mixture was allowed to stabilise and reach equilibrium for 15–20 minutes. Itraconazole-containing microemulsions were then kept at room temperature.[18]

2.5 Qualitative and Quantitative tests for ME

Dilution test

The dilution test was performed by diluting 1 ml of prepared ME(s) to 100 ml and observed for clarity/turbidity/phase separation. It is confirmatory test of microemulsion to know which type of microemulsion was formed.

Centrifugation

Centrifugation test was used to evaluate physical stability of microemulsions. Microemulsions were centrifuge (Remi Laboratories, Mumbai, India) at 5000 rpm for 10 min and system was evaluated for creaming or phase separation by visual observation.[19]

pH of microemulsion

pH of microemulsion was determined by using digital pH meter (Systronics).

Transmittance (%T)

The percentage transmittance of 2ML ME(s) was checked against distilled water using UV-VIS spectrophotometer at 650 nm.

Drug Content Studies

In a 50 ml volumetric flask containing methanol, a microemulsion equivalent to 5 mg of itraconazole was placed and swirled for 30 minutes. Methanol was used to increase the volume to 50 mL. The resulting solution was further diluted by 2 ml of methanol using a membrane filter of 0.45µm.The absorbance of the solution was measured spectrophotometrically (Shimadzu UV, Japan) at 262nm.[20]

Dispersion stability studies

For 30 minutes, the formulations were centrifuged at 3500 rpm. For the heating and cooling cycle, no phase separation formulations were used (freeze thaw cycle). Six cycles were performed in a hot air oven at temperatures ranging from 4°C (refrigerator) to 45°C, with storage at each temperature for at least 48 hours. For further research, the formulations that were stable at these temperatures were chosen.[15]

Transmission electron microscopy

Transmission electron microscopy was used to examine the morphology of itraconazole microemulsion (CM200, Philips, FEI Company). One drop of diluted samples was put on film-coated copper grids, dried, and studied under the electron microscope after being negatively stained with 2 percent phosphotungstic acid (PTA).[21]

Globule size and zeta potential measurements

The globule size and zeta potential were assessed using the zetasizer nano-zs (Malvern instrument). At a temperature of 25°C, the experiment was carried out. A 1ml sample was diluted with double distilled water.[22] The globule size and zeta potential were assessed using

the zetasizer nano-zs (Malvern instrument). At a temperature of 25°C, the experiment was carried out. Double distilled water was used to dilute a sample of 1ml.[22]

2.7 Preparation of ME based gels of ITZ

Distilled water was used to make blank gels of various polymers. In a nutshell, the polymer was dispersed in 100 mL distilled water and blended for 60 minutes using a mechanical mixer (Remi). For carbopol gels, triethanolamine was utilised as an alkalising agent.[23] For the ME preparation, the preservative was first thoroughly combined with a mixture of oil and Smix. The medicine, Itraconazole, was then dissolved in the aforesaid mixture at room temperature using magnetic stirring. Dropwise additions of double distilled water to the oily mixture were made until a clear and transparent microemulsion was formed. With mild magnetic stirring, the mixture was allowed to stabilise and reach equilibrium for 15–20 minutes. All itraconazole-containing microemulsions were then kept at room temperature.[18] The gels and microemulsions were combined in a 1:1 ratio.[24] The following table lists the formulation batches in detail. 1.

2.8 Characterization of ITZ containing ME based gels

Attenuated total reflectance – Fourier transform infrared spectroscopy

The infraround spectrophotometer of ITZ, ME, was utilised in order to get a reduced total reflectance-Fourier transform infraroad (ATR-FTIR) (Shimadzu, IR Affinity, Japan).The samples were delivered to the ATR compartment for analysis. At an average of 25 scans and a resolution of 4/cm, the spectra for the range 600-4000/cm were acquired.

Physical examination

Prepared ME based gel formulations were investigated for physical characteristics like colour, homogeneity and phase separation.[25]

Drug Content

Drug content of emulgel was measured by UV spectrophotometer. 1 gm of emulgel was diluted to 50 ml with methanol. 2ml of this solution was further diluted methanol. The absorbance of the solution was measured spectrophotometrically (Shimadzu UV, Japan) at 262nm.[26]

Spreadability study

1gm of itraconazole emulgel was placed in a 1 cm diameter circle pre-marked on a glass plate, which was then covered with a second glass plate to assess spreadability. The upper glass plate was permitted to rest for 5 minutes with a weight of 500 grams on it. The gel spreading was noted from the change in diameter of gel placed.[27]

Determination of pH

The pH of itraconazole emulgel was determined by using digital pH meter (Systronics), at ambient room temperature.[28] The calibration of pH meter was done with buffered solution before each use.

Rheological Studies

The viscosity of the different emulgel formulations was determined at 25°C using a cone and plate viscometer (Brookfield rheometer RS plus).[29]

In vitro drug release studies

A Franz diffusion (FD) cell was used in the in vitro drug release research (with effective diffusion area 3.14 cm2 and 25 ml cell volume). The formulation was applied to the FD cell's egg membrane, which was sandwiched between the donor and receptor compartments. As a dissolving medium, phosphate buffer pH 7.4 was utilised. A circulating water jacket kept the temperature of the cell at 37 0C. The solution was continuously stirred using a magnetic bead while the entire assembly was kept on a magnetic stirrer. As a control, a similar blank set was run at the same time. At appropriate time intervals, a sample (1 ml) was taken and replaced with equal volumes of fresh dissolving media. After proper dilutions, samples were tested for drug content using a UV visible spectrophotometer (Shimadzu UV1800). The total percentage of drug released was computed.[30]

3. RESULTS AND DISCUSSION

3.1 Solubility of ITZ

ITZ's physicochemical features indicate that it could be useful for topical medication delivery. Karanj oil (108.40±1.59) had the highest ITZ solubility among the selected oils that were examined, hence it was chosen as an oil. Tween 80 (246.62±16.08) demonstrated reasonable solubilizing capability for ITZ among the surfactants . ITZ is most soluble in the co-surfactant isopropyl alcohol (IPA) (Freely soluble).

Table 2: Solubility of itraconazole in various oils, surfactants and co-surfactants.

	Vehicle	solubility of itraconazole (mg/ml)
Oils	oleic acid	64.02±1.32
	Karanj oil	108.40±1.59
	Olive oil	25.68±1.37
Surfactants	Tween-20	190.12±17.12
	Tween-80	246.62±16.08
Co-surfactants	Isopropyl alcohol	Freely soluble
	Propylene glycol	151.89±18.3
	PEG-200	110.58±15.52
	PEG-400	125.65±16.3

3.2 Construction of Pseudoternary Phase diagram

The pseudoternary phase diagram of oil (Karanj oil)/IPA / Tween 80/ water system were constructed as shown in Figure. The region giving clear and transparent formulation was considered as the ME window and was marked in pseudoternary phase diagram. The best weight ratio of surfactant and cosurfactant (Km) was discovered to be 6:4, thus for subsequent investigation, the best surfactant combination (Smix) comprising Tween 80 and IPA in a 6:4 ratio was blended with the highest oil (Karanj oil).

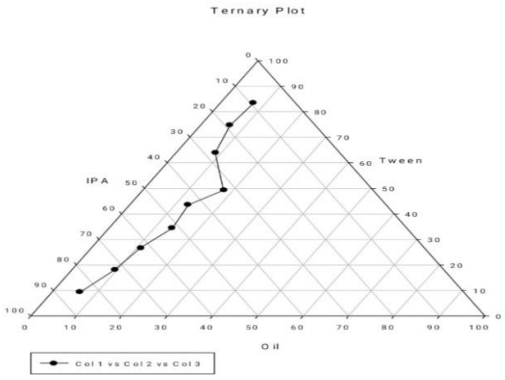


Figure 1: Pseudoternary phase diagram of the system containing Karanj oil, Tween 80, IPA and water.

3.3 Ternary Phase Diagram

The region of ME and concentration ranges of components used for formulation of ME were determined by phase studies. The effect of different surfactant /cosurfactant weight ratios on extent of stable ME region was also studied. The phase diagram of the system including oil, Smix, and water was created and is shown in fig. The microemulsion zone (ME region) in the figure is black, whereas the non-ME region is white. It is evident from the figure that tween80 and IPA could give considerable micro emulsification region (>40%).[15]

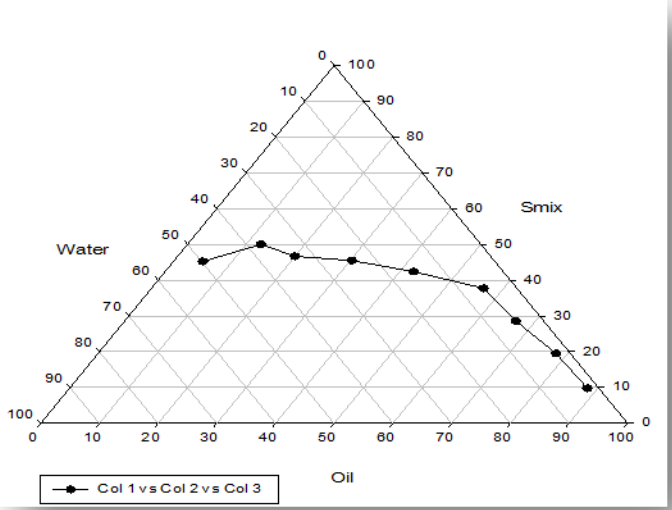


Figure 2: Phase diagram of the system containing Karanj oil, mixed surfactant and water.

3.4 Preparation of ITZ MEs

The Smix ratio with the highest ME region was chosen from the ternary phase diagram. When the weight ratios of Oil: Smix : water of 5:45:50 [M1], 10:45:45 [M2], and 10:50:45 [M3] were utilised, oil-in-water ME was generated.

3.5 Qualitative and quantitative tests of MEs

Results of qualitative and quantitave tests of all prepared MEs are given Tables.

Dilution Test

Except for formulation M1, all microemulsions generated showed phase separation and turbidity.

Centrifugation

Centrifugation test was performed to evaluate physical stability of micro-emulsions. Formulations M2 and M2 showed creaming /phase separation while other formulation was stable at centrifugation.

pH of microemulsion

The pH values of microemulsions were varied from the range 5.06 to 5.15 which was acceptable pH of skin.[31] This is an important parameter as the skin pH ranges between pH 5.0-6.5.

Transmittance (%T)

Transmittance for all formulations are given in table and found to be in the range of 71.2 to 98.3 %. Formulation M3 shows less transmittance due to turbidity while formulation M1 shows high transmittance due to clarity.

Drug Content Studies

Dispersion stability studies

The formulations M1 stable at these temperatures were selected for further studies.

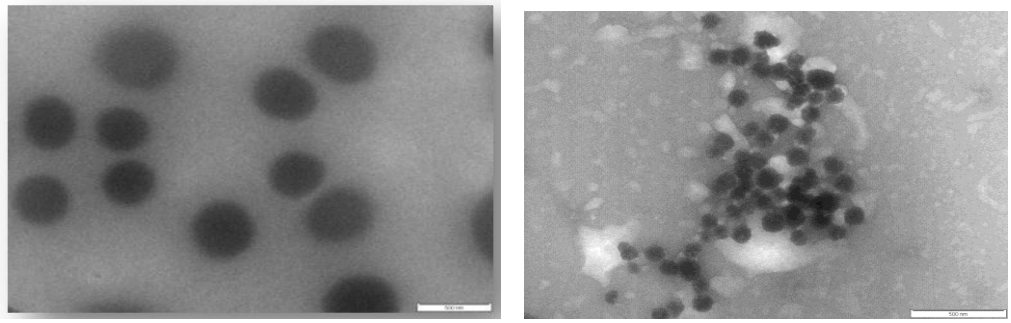
From above results the formulation M1 shows more stability than other formulations. So, M1 microemulsion was further incorporated into gelled base.

Table 3: Dilution, Centrifugation, pH, Transmittance, Drug content, Dispersion stability studies results.

Formulation code	M1	M2	M3
Dilution test	No phase separation	Phase separation	Phase separation
Centrifugation/ creaming	No	Yes	Yes
pH	5.15	5.11	5.06
Transmittance	98.3	75.5	71.1
Drug content	99.3	98.5	95.1
Dispersion stability	Stable	Unstable	Unstable

Transmission electron microscopy

In the transmission electron microscope, the globules of optimised ME seemed to be virtually spherical in shape. In the light environment, the globule appeared dark (Fig.).The average droplet size of optimized ME was 136.4 nm. The globule size of optimized ME increases as compared optimized blank ME.

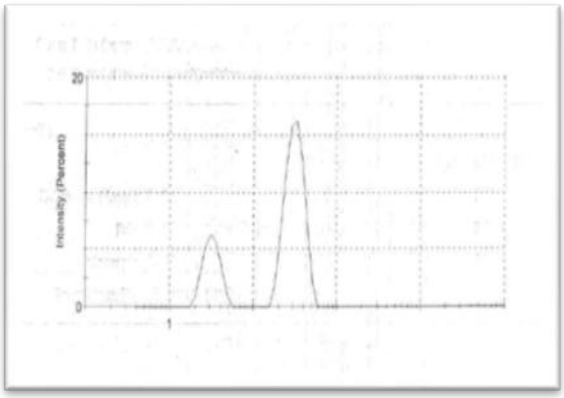


Test ME TEM **Blank ME TEM**

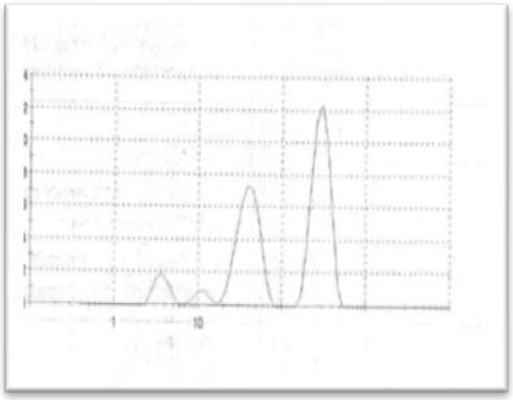
Fig 3: Transmission electron microscopy.

Measurement of globule size and zeta potential

Globule sizes of microemulsion were found to be 885.5dnm and 136.4dnm respectively test and blank ME formulations. The small globule size of microemulsion was due to large percent of Smix. Similarly, zeta potentials were observed to be -0.118mv and 0.00365mv respectively test and blank ME formulations.

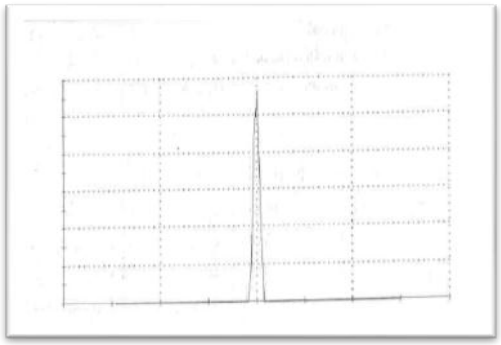


Itraconazole unloaded size distribution

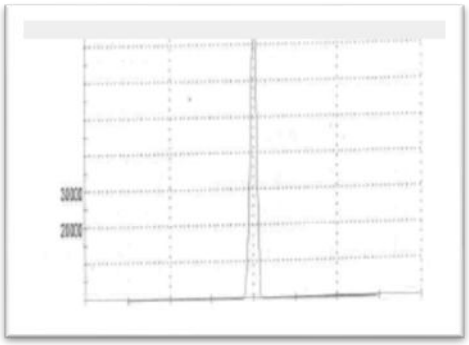


Itraconazole loaded size distribution

Figure 4: Globule size distribution.



Itraconazole unloaded zeta potential



Itraconazole loaded zeta potential

Figure 5: Zeta potential.

Table 4: Zeta potential and Globule size distribution.

Zeta potential		Globule size distribution	
Itraconazole unloaded ME (blank)	**Itraconazole loaded ME (test)**	**Itraconazole unloaded ME (blank)**	**Itraconazole loaded ME (test)**
0.00365	-0.118	136.4dnm	885.5dnm

Evaluation of ME gel

Melting Point

The melting point of itraconazole was found to be 166.2^{0}C. The reported melting point of drug was 166-170^{0}C.

FTIR Spectrum of Interoretation

Itraconazole's FTIR spectra revealed peaks at 1583.27 (C-N stretching), 1700.91 (C=O stretching), 1187.94 (C-H aromatic), 1141.65 (C-N stretching), 3440.39 (aromatic C-H stretching), 2927.41, and 2856.66 (C-N stretching) (aliphatic C-H stretching).

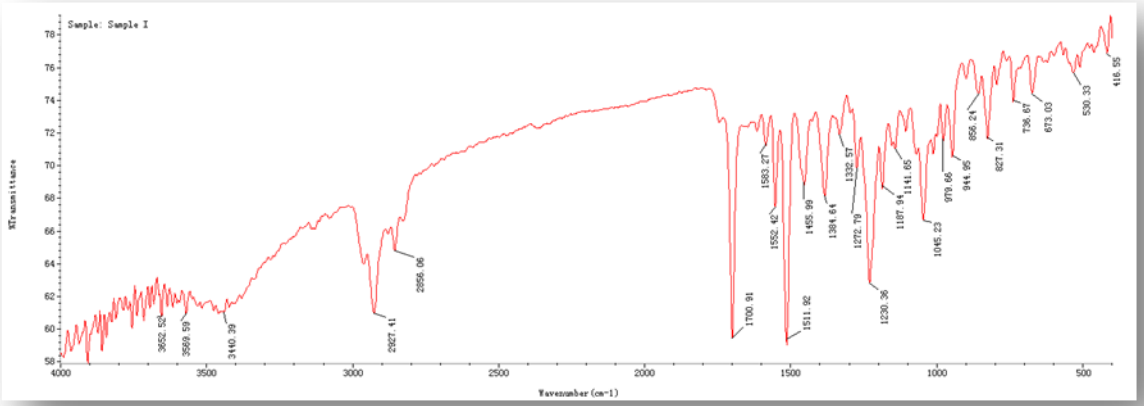


Fig 6: IR spectrum of Itraconazole.

Physical Examination

All ME-based gel formulations were white/buff thick creamy preparations with a smooth uniform texture and a glossy appearance.[33]

Drug content

Drug content was calculated using the equation, which was obtained by linear regression analysis of calibration curve of itraconazole in methanol. The drug content of all ME gel formulation was found to be 94-104%.[33]

Determination of pH

The pH values of microemulsions were varied from the range 6.09 to 6.34 which lies in the normal pH range of the skin.[34]

Spredability study

The Spreadability numbers suggested that the emulgel could be easily distributed with a minimal degree of shear. The spreadability of the gel is critical for patient compliance and aids in uniform application of the gel to the skin. A good gel will spread quickly and have a wide spreadability. ME gels prepared with low concentration of carbopol F1 belonged to fluid gel category, having more spreadability values. The stiff and semi stiff formulations were made with increasing concentrations of carbopol and xanthan gum, while the formulations F3 and F6 made with 1.5 g of carbopol were stiff and semi stiff. 1.5 g xanthan gum was classified as very stiff. The spreadability of formulations reduces as the concentration of gelling ingredient in the formulation increases.

Table 5: Spreadability studies.

Formulation Code	Drug content	pH	Spreadability gm.cm/sec
F1	102±0.14	6.1±0.69	1.06±0.2
F2	99±0.75	6.09±0.70	0.83±0.1
F3	103±0.25	6.11±0.57	0.56±0.12
F4	102±0.14	6.34±0.28	0.81±0.13
F5	100±0.15	6.19±0.35	0.76±0.17
F6	98±1.86	6.31±0.19	0.63±0.2
F7	101±0.12	6.14±0.29	0.96±0.14
F8	94±0.54	6.10±0.66	0.85±0.16
F9	99±0.6	6.12±0.48	0.96±0.10

Viscosity study

The viscosity results helped to understand the influence of various formulation parameters on consistency, spreadability and drug release. Generally consistency of formulations depends on the ratio of solid fraction to liquid fraction which produces structure.

The viscosities of ME based gels of itraconazole at low and high shear rate are given in table. Formulation containing CBP (F1-F3) exhibited high viscosity than other formulations. This is due to difference in the type of gelling agent which results in changing the structure consistency and low hygroscopicity of XG and mixture of polymers (CBP:XG), (CBP:CMC), (CBP:CMTG) (1:1) ratio as compared to CBP 934. Shear thinning was observed in all created formulations, as the viscosity was found to be reduced as the shear rate was increased (Table). Shear thinning occurs when shear is applied and the structure begins to break down when the sites of contact are disturbed and the polymeric chain aligns.Shear thinning

behaviour is a desirable property for the topically applied preparations. Since, all prepared formulations showed pseudoplastic behaviour indicates good spreadability.

Table 6: Viscosities of ME based gels of itraconazole.

Formulation code	η* max (cP)	η** min (cP)
F1	350.47	224.36
F2	1588.24	680.96
F3	1493.45	418.39
F4	58.67	15.6
F5	1063.92	223.44
F6	1543.49	304.62
F7	1047.47	417.28
F8	868.69	332.65
F9	776.43	292.85

*****Viscosity at high shear rate (100 rpm); ******Viscosity at low shear rate (11.5 rpm).

In vitro drug release

All the batches of itraconazole ME gels showed drug diffusion within the range of 58.57±1.48% to 96.66±1.89% at the end of 6h.

The (CBP: CMTG) (1:1) containing gels showed maximum 96.66±1.89% drug release at the end of 6h. (CBP: CMTG) (1:1) gels exhibited higher drug release in comparison with gels formulated with CBP, XG and mixture of polymers (CBP: XG), (CBP: CMC) (1:1) ratio. As the concentration of CBP was increased in formulations (F1-F3) drug release was found to be decreased. This may be attributed to increased viscosity of carbopol gels.

Due to the difference in viscosity of the polymers, when the concentration of gelling agents in formulations increases, the diffusion of formulations reduces.

The in-vitro release of prepared formulation compared with marketed formulation (Itratrox gel 1% w/w). From the comparison it was observed that formulation F9 shows 96.66±1.89% drug release at the end of 6h and marketed Itratrox gel (1% w/w) shows 90.56±1.75% drug release at the end of 6h. From the result it was observed that ITZ ME gel of F9 batch shows more drug release compared to the marketed formulation.

Table 7: Formulation drug release percentages in Phosphate Buffer (Ph 7.4) for Formulation batches F1-F6.

Time (hr)	F1	F2	F3	F4	F5	F6
0	0.00	0.00	0.00	0.00	0.00	0.00
0.5	11.95±1.09	1.9±2.56	1.6±3.17	4.6±3.17	2.28±1.22	1.80±1.26
1	18.09±0.93	10±1.85	2.80±1.17	14.80±1.17	6.47±1.32	3.90±2.69
2	23.80±1.52	17.14±1.62	6.61±0.91	28.61±0.91	16.85±1.56	8.90±2.17
3	34.85±1.75	30.47±1.43	12.61±1.31	47.61±1.31	29.09±1.23	15.42±0.67
4	52.85±2.2	43.33±1.58	27.61±1.63	57.61±1.63	46.23±2.10	27.46±1.84
5	64.23±1.21	56.19±1.28	41.80±1.56	64.80±1.56	58.09±2.30	42.19±1.04
6	71.21±1.13	66.66±1.89	58.57±1.48	78.57±1.48	75.23±1.56	69.52±1.42

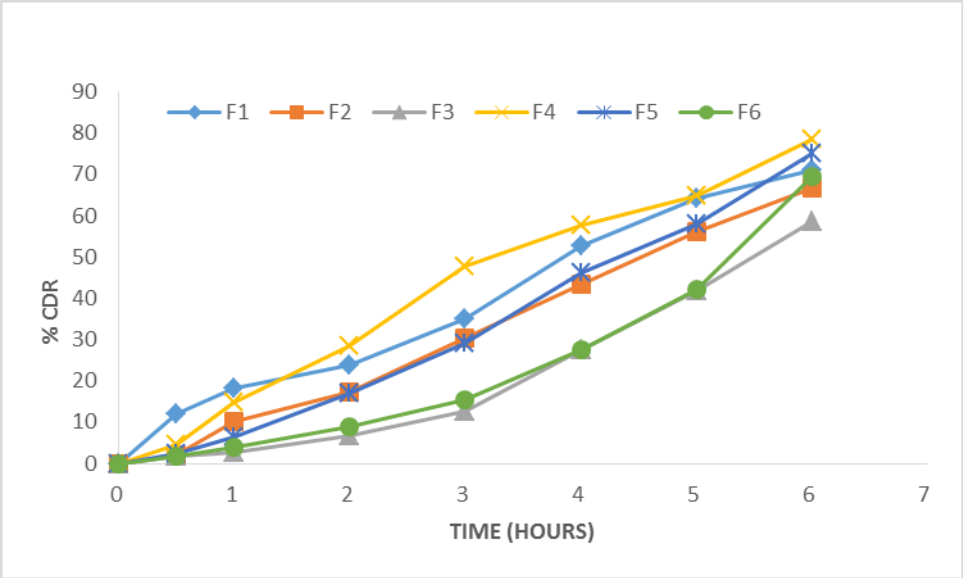


Figure 7: Formulation batch F1-F6 percentage medication release in Phosphate Buffer (Ph 7.4).

Table 8: Formulation drug release percentages in Phosphate Buffer (Ph 7.4) for Formulation batches F7-F9.

Time (hr)	F7	F8	F9	Standard
0	0.00	0.00	0.00	0.00
0.5	4.28±2.31	6.28±1.91	6.0±2.56	5.18±1.58
1	13.42±1.91	23.18±1.22	24±1.85	20.46±1.20
2	24.47±1.13	36.90±1.12	37.14±1.62	34.40±1.56
3	28.52±1.59	40.76±1.49	60.47±1.43	54.80±1.40
4	46.33±1.87	52.38±1.13	83.33±1.58	72.62±1.90
5	62.57±1.65	75.66±1.94	86.19±1.28	81.72±1.48
6	67.61±2.60	82.85±1.16	96.66±1.89	90.56±1.88

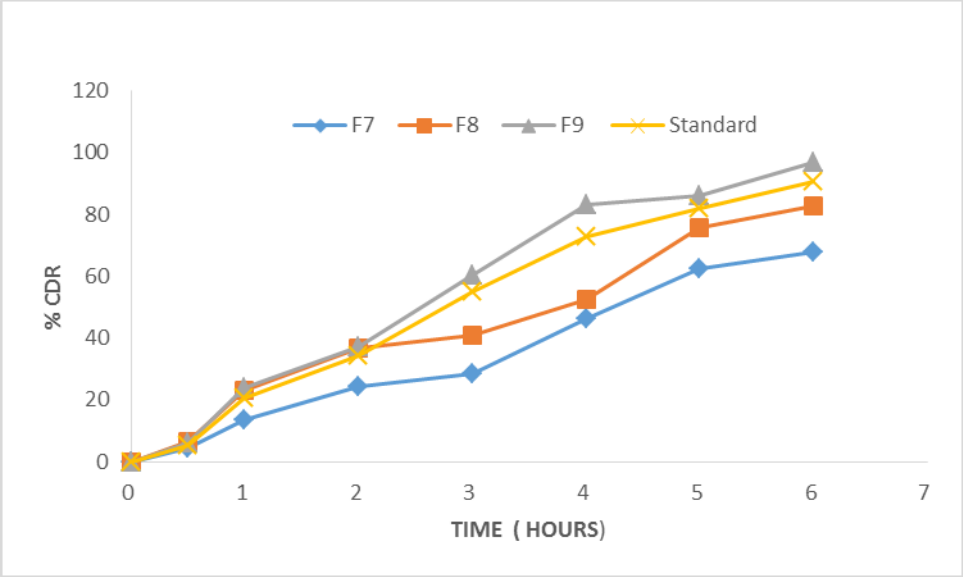


Figure 8: Percentage Drug Release of Formulations in Phosphate Buffer (Ph 7.4) for Formulation batch F7-F9.

4. CONCLUSION

ME gel produced with oil (5%), S/Cos (45%), water (50%) and (CBP: CMTG) (1:1) outperformed all other formulations in terms of overall formulation quality. Developed microemulsion system provides solubilization of hydrophobic drug, thus impart availability of itraconazole in formulation, where as globule size and zeta potential was 885.5dnm and-0.118, respectively, indicating the stability and proper formulation of microemulsion. The prepared ME gel can be considered as cost effective formulation because of reduction of topical dose of itraconazole in formulation. The F9 batch had the highest release (96.66±1.89). The prepared microemulsion gel show better release profile than marketed preparation. Furthermore, they were shown to have a better permeation and look.. It was a shear thinning system because all formulations exhibited non-Newtonian pseudoplastic behaviour. Thus, the results of this research study clearly indicated a promising potential of the itraconazole ME gel as an alternative to the conventional dosage forms.So itraconazole ME gel can be used as an anti- fungal agent for topical drug delivery.

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6. CONFLICT OF INTEREST

All authors approve the final manuscript and declare that there are no conflict of interests.

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