Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/15409
DOI URL: http://dx.doi.org/10.21474/IJAR01/15409

*RESEARCH ARTICLE*

# FORMULATION AND EVALUATION OF ANTIFUNGAL MICRO EMULSION-BASED GEL FOR TOPICAL DRUG DELIVERY USING MILLETIAPINNATA

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## *Manuscript Info*

***Manuscript History***
Received: 18 July 2022
Final Accepted: 20 August 2022
Published: September 2022

***Key words:-***
Itraconazole, Micro-Emulsion-Based Gel, Pseudo- Ternary Phase Diagram, Topical Drug Delivery

## *Abstract*

Firstly,we are study to formulate and test a topical gel containing of Itraconazole micro- emulsion (ITZ). The Formulation of micro emulsion researchis necessary to study before it's thepreformulation study of micro emulsion of Itraconazole. To estimatethe maximal solubility of ITZ in oils, surfactants and co- surfactants were investigated to estimatefilling material potential. In reference to the micro- emulsion region, with Karanj oil as the oil phase, the use of surfactant as a Tween-80 and use as aDiamethyl Carbinol Or (IPA) as the Another surfactant to improve its performance, a pseudo- ternary phase diagram was created. If using of Carbopol 934, Xantumgum, carboxymathylcellulose,Carboxymethyl -Tamarind gum (CMTG (CMC) That may be increased or improved its qualitative & Quantitative test .ME is evaluate by % transmittance, Viscosity, pH,particle-Size, zeta potential, Physical appearance, Drug content, pH,spreadability, viscosity, in -vitro release. If we take a oil as like karanj oil in the form of oil phase and using of a surfactant as like Tween 80 that may be obtain -Stable ME & useco-surfactant as an IPA, the weight ratio of 5:45:50. The evaluate ME based gel which is pH range between in (6.0- 6.34),and the Spreadability rangeis between (0.56-1.06) gm.cm/sec. The consistency or viscosity examination intimated pseudo- plastic performance of all ME based gel formulations.In the midest the examination ME gels If we are using of CBP: CMTG containing gels that may be we obtain greater maximum drug release at the end of 6h incomprising to other marketed.



## Introduction:-

Almost two-thirds of the world's population is infected with a common fungal infection.[1] Fungal infection is a constantly infection that affects two-thirds of the world's population. In last few years, the morbidity of fungal contagious caused by fungi including Candida, Aspergillus, and Cryptococcus has increased. A skin disease caused by mycosesas fungus. An part of human body skin infection caused by Candida, but they're most common in skin surface areas, where two skin rebuild rub or touch. [2,3]

Itraconazole (ITZ) its activity as Triazoleantifungal. It's a cure from the BCS class II.In conventional dose, bioavailability of Itraconazole formulations is around 15-20%. It is a 6-hour biological half-life. Constipation, abdominal pain, headache, and, in rare cases, heart failure has all been reported as side effects of ITZ. The side effect

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of ITZ as like allergy, reaction, symptom in patients with kidney related and/or liverwort injury is likewise a liability. [4,5]

Topical cure, such as creams and ointments, are gummy and need rubbing, which can make patients disturbed. Respectively of their multiple advantages over other paste like preparations, gels have gained remarkable in both the pharmaceutical and cosmetic fields.[6]Gels is a semisolid preparation in which the dispersion medium's moment is limited by interlacing three-dimensional networks of particles. They are immunological and patient-friendly, are non-fatty, and can be easily washed from the skin. They are also inexpensive, have a bounded action with few side effects, improve the medicine absorption, and its decrease dose frequency, and stable drug spread design. [6,7] despite of the many benefits of gels, its important disadvantage is the delivery of hydrophobic medicines. When using of micro-emulsion based is breaking a barrier of hydrophobic moiety for special character of gel.[8]

Micro- emulsions (MEs) have built up in demand and application in recent years due to their incomparable properties. We are using or prepared or study in as a pharmaceutical Industries, laboratories, as well as academic researchers, have shown an interest in these compounds, which is using of variety of various methods for preparing of micro-emulsion gel. To improve the its dissolving efficacy in both water-loving and oil loving. If we make a stable emulsion, and its increasing drug permeability.[9]ME'shaslow viscosity, on the other hand, makes it toodifficulttoapply to skin and reduces pain compliance.] if we improve compared with a solution, gel, or formulations, MEs or ME gels improve rapidly. Natural polymers are cost-effective in distribution systems because they are readily available. They're also environmental, micro- porous, and easily accepted by regulatorybodies.[11]

We are using as a Polymers including carbopol (CBP), Hydroxypropyl methylcellulose (HPMC), carboxymethyl-tamrind gum (CMTG), carboxymethyl cellulose (CMC), and in the preparationof ME gels, Xanthum gum is used as a natural polymer.AKaranjoil is use as a plant of pongaminapinnata seed, a non-edible semi-drying fixed oilitsderivedfrompongaminapinnataplantbelonging to the Leguminosaefamily, it is a natural oil.[9] According to the literature, it is a therapeutic oil that is mostly used to treatment of itches, abscesses, and skin problems.[10] appropriately, Karanj oil can be apply of micro emulsion gel as an oil phase in the preparation of topical drug delivery system inmicro emulsion-gels. theyare weakly water soluble and improvetheabsorption and prolonging drug release.

Therefore, it is to develop for better hydrophobic drug deliveryandusing of ME including topical gels forCBP, XG, TG, CMTG, and CMC for better hydrophobic drug delivery. IF again research to develops the viscosity properties and drug release of the produced gels.

## Materials And Methods:-

**Materials:**

Aurochem Pharmaceuticals Pvt. Ltd., Palghar, give ITZ. Lobachemie, Mumbai, give 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 LobaChemie in Mumbai and were of analyticalquality.

**Table 1:-** Formulation of micro-emulsion 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 |

**Solubility study of ITZ**

We use andselect of oils and excipients because due to to high solubility in itraconazole. Based on the literature analysis, Karanja oil was chosen as an efficient excipient for micro- emulsion formation.

We select in several oils as like(Karanj oil, Olive oil, Oleic acid) for the good solubility inItraconazole drugwas studied to estimate the best oil for usage as the oil phase in micro- emulsion. We using of several surfactant as like (Tween-20 and Tween-80) for Itraconazole solubility and using as a co -surfactants (Isopropyl alcohol, propylene glycol PEG-200, PEG-400) was also investigated. In Stoppardvials (capacity 10mL), an extra amount of Itraconazole was adding to 3mL of the specified oil, surfactant, and co surfactant, and then primary mixing was carried out over magnetic stirrer for a few minutes. These vials were then held at 37 0.5 C for 72 hours in a mechanical bath shaker. Thenceforth using a sample which is , equilibrated were centrifuged (Remi) for 15 minutes at 3000 rpm. And after that a supernatant sample is found and collect it and membrane is filtered andspectrometric sample measurements at 262nm.And examinesolubility after proper dilution by methanol. Each experiment was repeat out threetimes.[15]

**Construction of pseudo- ternary phase diagram**

We using as the differencebetween fraction of mixed surfactant making in the building of a phase diagram, and the surfactant and co surfactantoptimal ratio (Km) was calculating using the micro emulsion area. Km was explore using a simple pseudo ternary phase diagram. The generation of micro emulsionsusing a four-component system consisting of an oil phase, a non-ionic surfactant, a co surfactant, and purified water was look over usingpseudo ternary phase diagrams (aqueous phase).

We using as a titration of homogeneous liquid mixes of water, surfactant, and co surfactant with oil phase at climate temperature yielded the pseudo ternary phase diagram. Surfactant and co-surfactant were combined in ratio is between ( 1:9 to 9:1) . we are using of nine samples which is independently with water, and then the oil was adding by help of droplet by droplet in to the mixture. Water content was set at 2.0 gm, and the total amount of surfactant and co-surfactant was also set at2.0 gm. To allow and standing for balance, samples were shaking 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 micro emulsion 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 co surfactant formed the pseudo ternary phase diagram.[16]

**Construction of Ternary Phase Diagram**

We are the firstly choose of ideal surfactant and co-surfactant weight ratio (Km) . The contents of mixed surfactant and oil in the mixtures varied from 9:1 to 1:9. A homogeneous oil surfactant– co surfactant 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. We putting The total amount was kept at 1.0 g. and further addition drop by drop purified water mixing in each mixture. To allow and stand for equilibration, samples were shaking 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]

**Preparation of ITZME:**

Firstly we select the largest micro emulsion region in between oil and Smix ratio. We select. The Oil and Smix were blended in various amount. A mixture of oil and Smix is dissolved in Itraconazole at room temperature using of magnetic stirring. And further using addition drop by dropof distilled to the oily mixture is make as a clear transparent emulsion is obtain or formed. With mild magnetic stirring, the mixture is allowed to steady and balanced toreach equilibrium for 15–20 minutes.And micro-emulsion of Itraconazole is kept in room temperature.[18]

**Qualitative and Quantitative tests for ME Dilution test:**

We are using of The dilution test was performed by dilution and preparing a micro emulsion I ml to 100 mland detect for clarity/turbidity/phase separation. It is a test of micro- emulsion confirmatory to know which type of micro emulsion was formed.

**Centrifugation:**
We study and evaluate of The physical stability of micro-emulsion by Centrifugation test.andusing a centrifuge which is make by (Remi Laboratories, Mumbai, India),) at 5000 rpm for 10 min and system was evaluate for creaming or phase separation by visualinspection.[19]

**pH of micro- emulsion**
We are using as a pH meter for micro-emulsion(Systronics).

**Transmittance (%T)**
We are study of the percentage transmittance of 2ML ME(s) which is checked in against distilled water checked using UV- VIS spectrophotometer at 650 nm.

**Drug Content Studies**
We are taking a volumetric flask which capacity is 50 ml containing methanolvolumetric, a micro-emulsion equal to 5 mg of Itraconazole was taken and placed for shaking for for 30 minutes. Using of Methanol volume up to make to increase volume 50 mL. and further that obtain resulting solution and 2 ml filtrate is dilution to 50 ml using of methanol .The absorbance of the solution was measured spectrophotometrically (Shimadzu UV, Japan) at 262nm.[20]

**Dispersion stability studies;**
We are taking using or making of micro-emulsion formulation which is centrifuged at 3500 rpm for 30 minutes. And there is a no phase separation formulation were used (freeze thaw cycle) for heating and cooling cycle. A hot air oven using which is temperatures ranging from 4°C (refrigerator) to 45°C for six cycle, with storage at each temperature for at least 48 hours. For further research, the formulations that were absolute at these temperatures were chosen.[15]

**Transmission electron microscopy**
We are study for morphology of micro-emulsion.it is necessary to using ofTransmission electron microscopy (CM200, Philips, FEI Company) for morphology of micro-emulsion. We are a take One drop of diluted samples was putting 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**
We are study and evaluate of The globule size and zeta potential using the zetasizernano-zs (Malvern instrument). Which is a temperature of 25°C, the experiment was performed. And 1ml sample was diluted into double distilled water.[22

**Preparation of ME based gels ofITZ:**
We are using of Distilled water to make to blank gels of various polymers. A polymer use as a nutshell which is dispersed in 100 mL distilled water and blended them for 60 minutes usingamechanical mixer (Remi). We are using an alkalizing agent as likeas a Triethanolamine For preparation carbopol gels. We are using a preservative a mixture oil and Smix for making or preparation ME,. The medicine, Itraconazole, was then dissolved in the aforesaid mixture at room temperature using as a magnetic stirrer. And further that addition of distilled water drop by drop to make a clear solution and transparent micro emulsion was formed.

With mild magnetic stirring, the mixture was allowed to obtain and reach equilibrium for 15–20 minutes. We are capt all formation of Itraconazole micro emulsion at a room temperature. and micro emulsions were combined in a 1:1 ratio.[24] The following table lists the formulation batches in detail.1.

**Characterization of ITZ containing ME basedgels:**
Attenuated total reflectance – Fourier transform infrared spectroscopy

We are using total reflectance-Fourier transform infrared (ATR-FTIR) (Shimadzu, IR Affinity,Japan). For the complete analysis.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 wereacquired.

**Physical examination**
We are using of natural examination and investigated of formulations of mico-emulsion for Natural quality as like colour, identity and phaseseparation.[25]

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

**Spreadability study**
We are taking 1gm of Itraconazoleemulgel in a 1 cm diameter circle pre-marked on a glass plate, which is covered by 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 gelplaced.[27]

**Determination of pH**
We are determinedThe pH of Itraconazoleemulgel 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:**
Using of A Franz diffusion (FD) cell in the in vitro drug release research (with effective diffusion area 3.14 cm2 and 25 ml cell volume). The formulation was carried by 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 utilized. 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 substitue 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 wascomputed.[30]

## Results And Discussion:-

**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 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) (Freelysoluble).

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

| | **Vehicle** | **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 |

**Construction of Pseudo ternaryPhasediagram**
The pseudo ternary 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 pseudo ternary phase diagram. The best weight ratio of surfactant and co surfactant (Km) was discovered to be 6:4,

thus for subsequent investigation, the best surfactant combination (Smix) comprising Tween 80 andIPA in a 6:4 ratio was blended with the highest oil (Karanjoil).

**IPA and water**

**Ternary PhaseDiagram**

The region of ME and concentration ranges of components used for formulation of ME were determined by phase studies. The effect of different surfactant /co surfactant 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 micro emulsion 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]

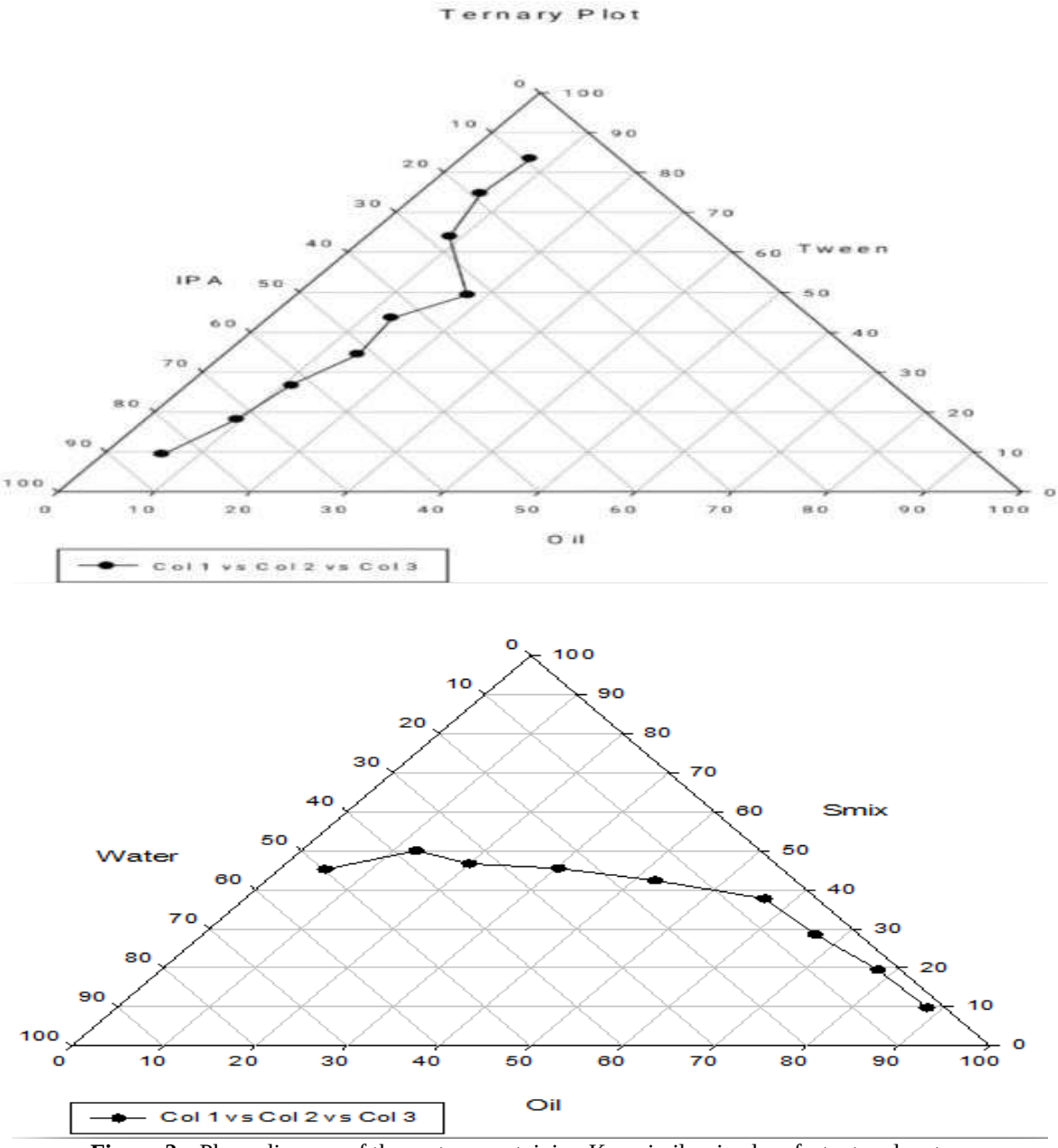



**Figure 2:-** Phase diagram of the system containing Karanj oil, mixed surfactant and water.

**Preparation of ITZMEs**

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 utilized, oil-in-water ME was generated.

**Qualitative and quantitative tests ofMEs**
Results of qualitative and quantitave tests of all prepared MEs are given Tables.

**Dilution Test**
Except for formulation M1, all micro- emulsions 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 micro emulsion**
The pH values of micro emulsions 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.

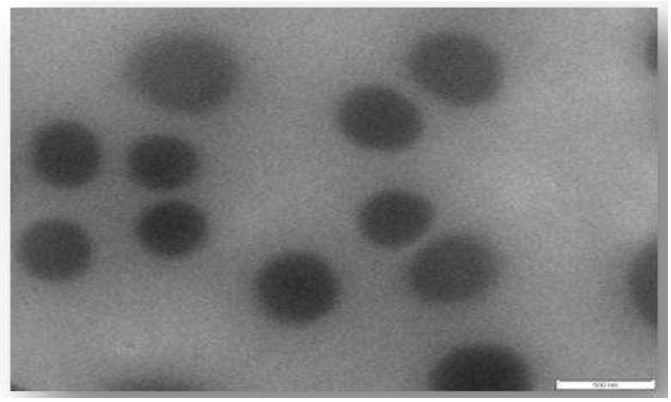
**Drug Content Studies Dispersion stability studies**
The formulations M1 stable at these temperatures were selected for further studies.From above results the formulation M1 shows more stability than other formulations. So, M1 micro emulsion was further incorporated into gelled base.

**Table 3:-** Dilution, Centrifugation, pH, Transmittance, Drug content, Dispersion stabilitystudiesresults.

| **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 optimized 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.

**TestMETEM**



**Blank ME TEM**

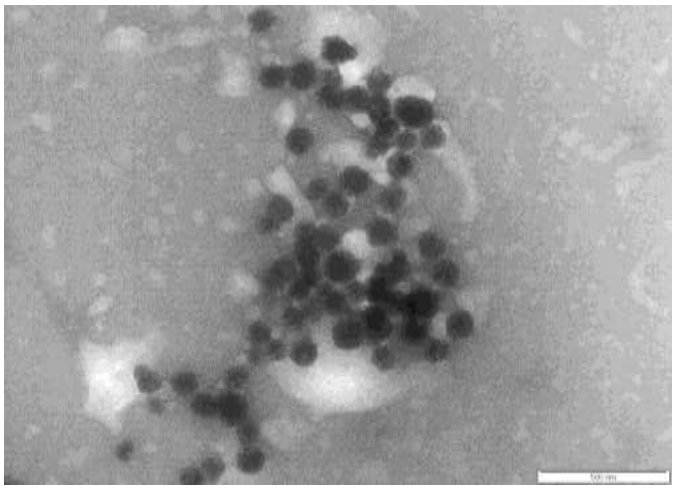
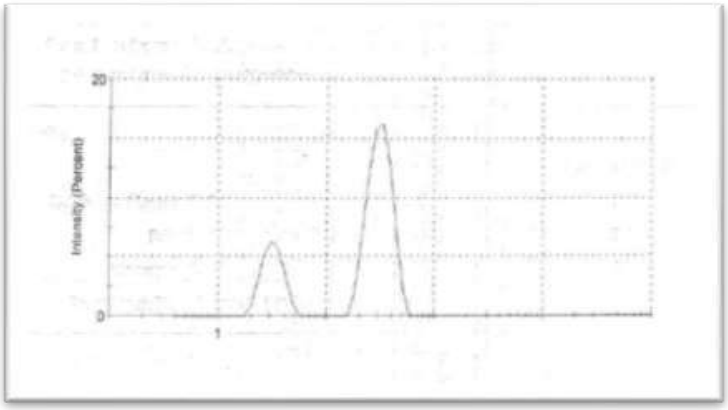


**Figure 3:-** Transmission electron microscopy.

**Measurement of globule size and zeta potential**

Globule sizes of micro emulsion were found to be 885.5dnm and 136.4dnm respectively test and blank ME formulations. The small globule size of micro emulsion was due to large percent of $S^{mix}$. Similarly, zeta potentials were observed to be -0.118mv and 0.00365mv respectively test and blank MEformulations.

**Itraconazole unloadedsizedistribution**




**Itraconazole loaded size distribution**

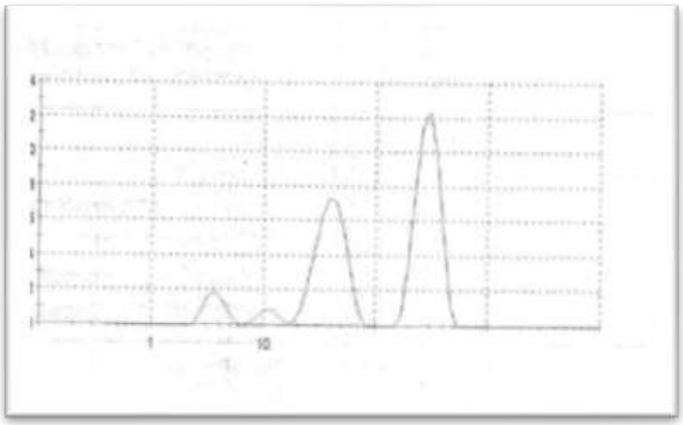



**Figure 4:-** Globule sizedistribution.

**Itraconazole unloadedzetapotentialItraconazoleloaded zeta potential**

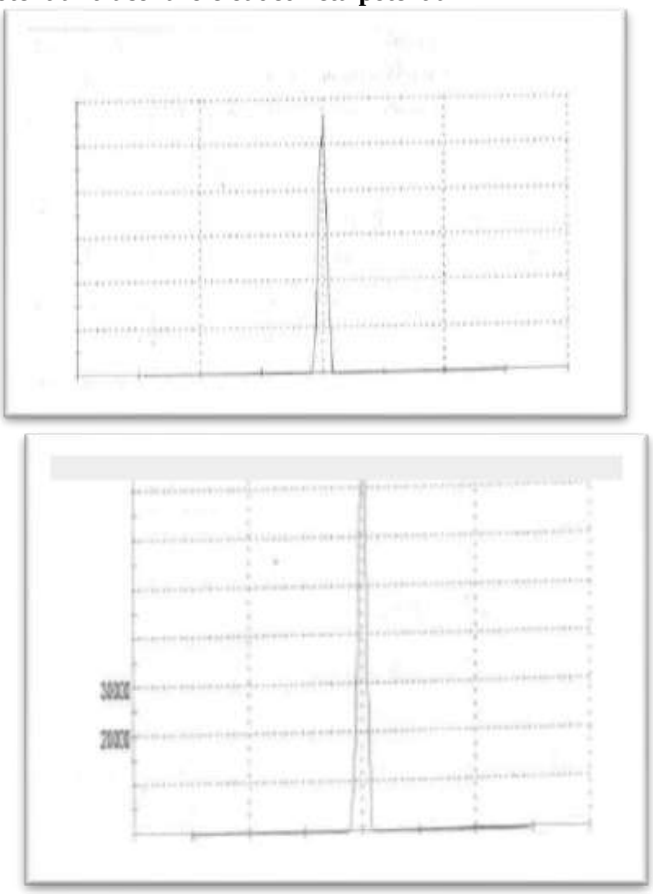


**Figure 5:-** Zetapotential.

**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 Interpretation**

Itraconazole 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).

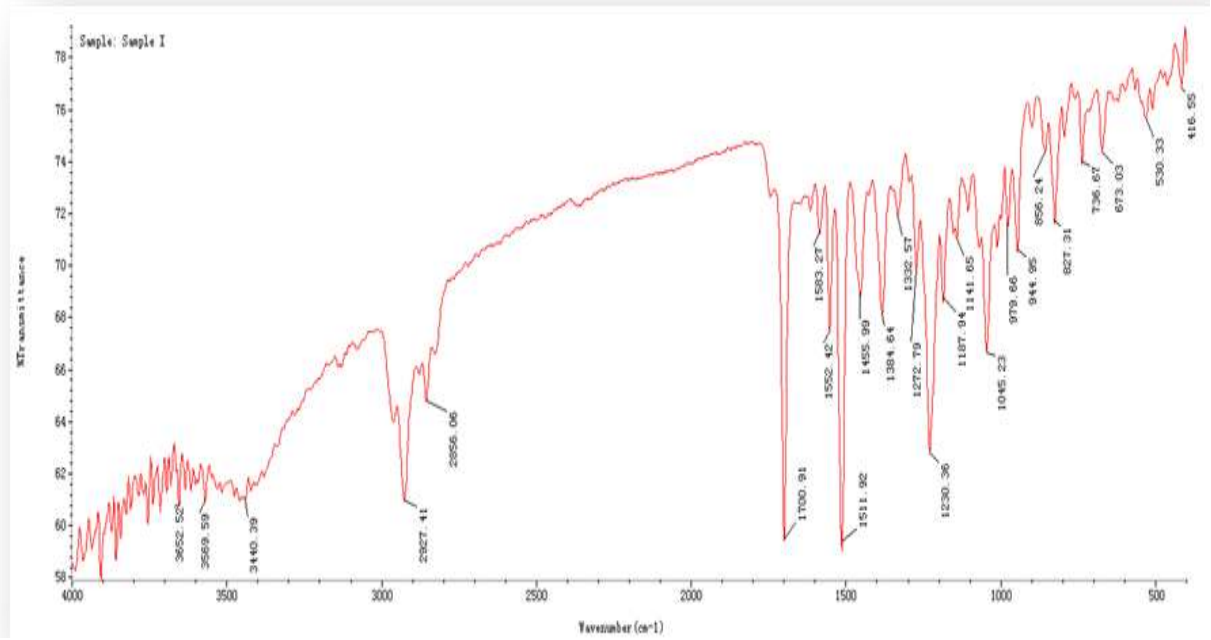



**Fig 6:-** IR spectrum ofItraconazole.

**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 micro emulsions were varied from the range 6.09 to 6.34 which lies in the normal pH range of the skin.[34]

**Spreadability 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 formulationincreases.

**Table 5:-** Spreadability studies.

| **mulation 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 consistency conclusion support to appreciation the effect of various preparation parameters on consistency, spreadability and drug release. Generallyconsistency of preparation based on the ratio of solid fraction to liquid fraction which producesstructure.

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 whenthesitesofcontactaredisturbedandthepolymericchainaligns.Shearthinning

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

**Table 6:-** Viscosities of ME based gels of Itraconazole.

| **Formulation code** | *** max (cP)** | **** 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:**
Itraconazole of all batches 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 enlarge in formulations (F1-F3) drug release was found to be Diminished. This may be attributed to increased viscosity of carbopol gels.

Due to the between in consistence of the polymers, when the immersion of congealing agents in formulation increases, the diffusion of preparation 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 Itratroxgel(Elkos Health Care) (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 marketedformulation.

**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 |

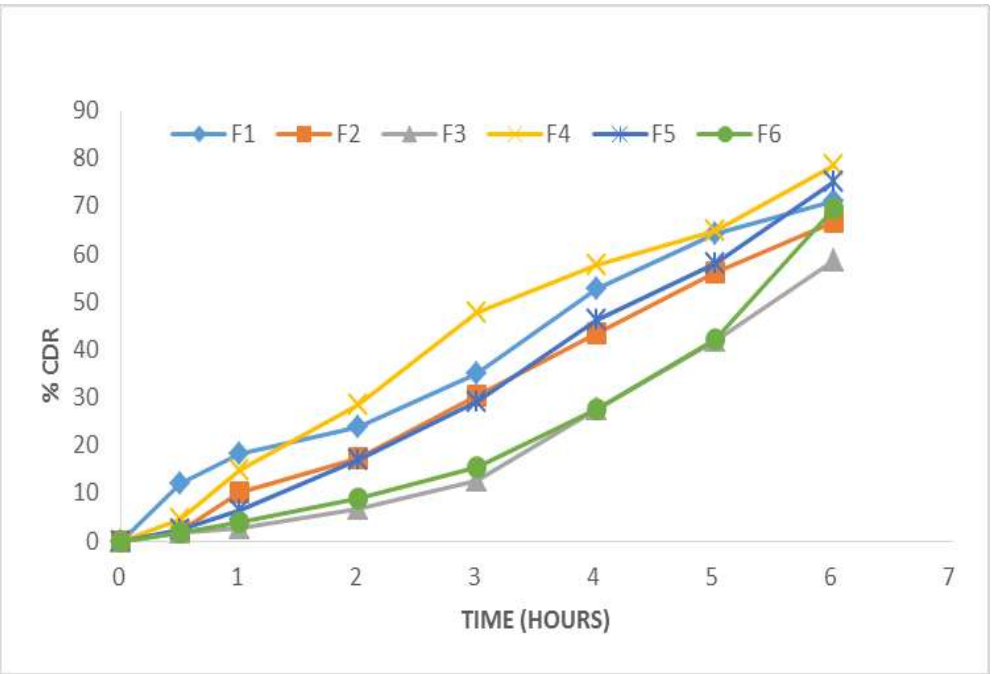



**Figure 7:-** Formulation batch F1-F6 percentage medication release in Phosphate Buffer (Ph 7.4).

**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 |

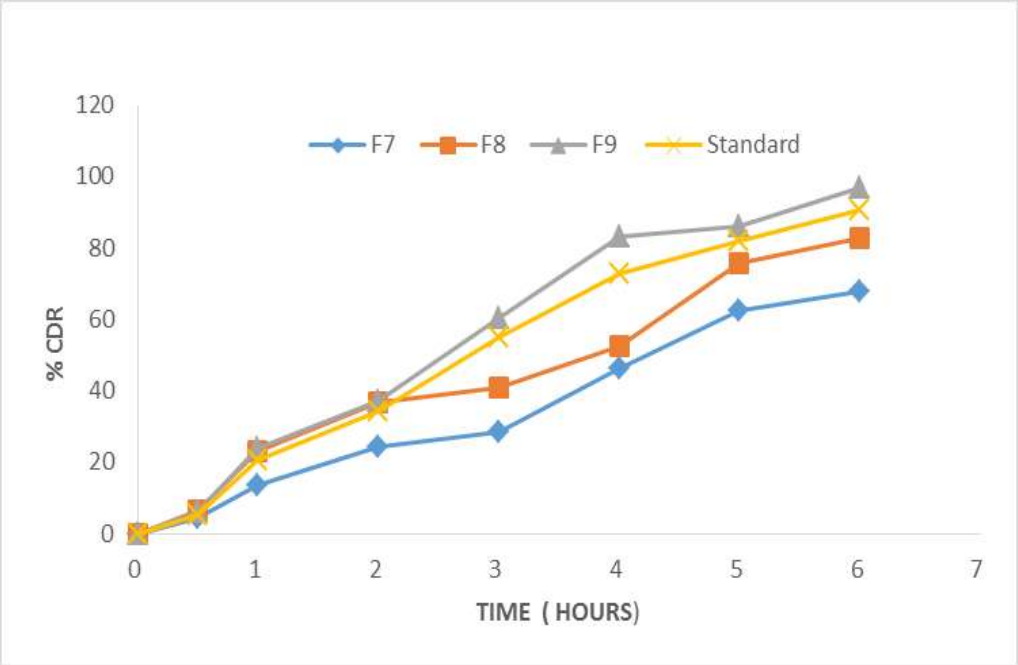



**Figure 8:-** Percentage Drug Release of Formulations in Phosphate Buffer (Ph 7.4) for Formulation batch F7-F9.

## 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 micro emulsion system delivers

Digestion of hydrophobic drug, thus allow obtain ability of Itraconazole in formulation, where as globule size and zeta potential was 885.5dnm and- 0.118, corresponding, remarking the strength and proper formulation of micro emulsion. The planned ME gel can be deal with as worthwhile formulation because of reduction of topical dose of Itraconazole in formulation. The F9 batch had the highest release (96.66±1.89). The prepared micro- emulsion gel show better release profile than marketed preparation. Furthermore, they were shown to have a better permeation and look..Itwas a shear thinning system because all formulations produced non-Newtonian pseudoplastic performance. Thus, the results of this research study clearly indicated a promising potential of the Itraconazole ME gel as an substitute to the traditional dosage forms.

Itraconazole ME gel maybe used as an anti- fungal emissary for topical drugdelivery.

## Acknowledgements:-

Aurochem Pharmaceuticals Pvt. Ltd. is grateful to the authors for their support. Ltd. for sending an Itraconazole sample as a gift.And **Prof.D.kvishwakarmaH.O.D.of pharmaceutics** in **K.I.P.M** Gorakhpur to give me laboratory facilities and co- operation my research and also gratefull thank **for DR.J.N.Mishra** director of pharmacy in **K.I.P.M Gorakpur** to support me .and help my work,.

**Conflict Ofinterest**

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

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