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Preparation and Evaluation of Efinaconazole Loaded Microemulsion with Tea Tree Oil

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ABSRTACT:
Aim: The present investigation was aimed to study the antifungal effect of Efinaconazole along with Tea tree oil to be prepared as microemulsion and explore the synergistic antifungal effect.
Method: Microemulsions were prepared by titrating different ratio of oil to Smix (Surfactant + Co-surfactant) with water and microemulsion region was recorded in the Pseudoternary phase diagram. Microemulsion preparations were characterized for compatibility, transmittance, viscosity, pH, % drug content, surface morphology, globule size and zetapotential, In-vitro drug release and stability studies. The microemulsion gel was prepared for optimized microemulsion preparation TTM3 by incorporated into 1% w/w Carbopol gel and evaluated for various parameters like spreadability, viscosity, pH, drug content, Invitro drug release and the In-vitro antifungal effect was carried out for the drug, oils, TCM3 and TTM3-G1 preparations.
Results: Prepared microemulsion and microemulsion gel were evaluated for various parameters which showed better results. In-vitro antifungal study confirmed that when Efinaconazole is combined with Tea tree oil in the form of microemulsion have shown synergistic antifungal effect compared with drug and oil separately.
Conclusion: Tea tree oil-based Efinaconazole microemulsion were prepared for topical application. TCM3 formulation taken as an optimized formulation because of high % transmittance, less viscous, high drug content and shows topical pH, more In-vitro drug released and good stability. In-vitro antifungal effects studied on Trichophyton rubrum fungal strain. Microemulsion drug delivery system can improve therapeutic effect of the topical drugs and combination of drug and essential oils in the form of microemulsion showed synergistic activity and give better therapeutic effect for topical drug delivery.

KEY WORDS: Microemulsions, onychomycosis, Efinaconazole, tea tree oil.

I. INTRODUCTION:

Onychomycosis is a fungal infection of the fingernails or toenails that results in discoloration, thickening, and separation from the nail bed. Onychomycosis occurs in 10% of the general population but is more common in older adults; the prevalence is 20% in those older than 60 years and 50% in those older than 70 years. Onychomycosis affects toenails more often than fingernails because of their steady growth, reduced blood supply, and frequent confinement in dark, moist environments. Onychomycosis is caused by various organisms, commonly dermatophytes of the genus Trichophyton. Treatment of onychomycosis is not easy task because of poor drug delivery to nails, nails are made of keratin, which is nonvascular and impermeable to many agents. Antifungals from the azole and allylamine classes are the most widely used oral medications (Itraconazole, Fluconazole, Ketoconazole.) these oral drugs have some safety problems, including impaired liver function and drug interactions, rendering them unsafe to use in some elderly patients for the treatment of onychomycosis. So, several topical agents are used for the treatment of onychomycosis. Ciclopirox 8% solution is the unique topical prescription medication available in the United States for the treatment of onychomycosis. But it includes some Adverse effects like burning, itching, and stinging at the application site. It may be used in patients who cannot take oral antifungals.[1]. the first topical triazole antifungals solution exclusively formulated for onychomycosis, 10% Efinaconazole, was approved in Japan in July 2014. Efinaconazole is an ingredient discovered in Japan that has low affinity to keratin, the main constituent of nails. This means that Efinaconazole has superior nail

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permeability and antifungal activity in the nail plate and nail bed.[2] However, due to poor nail permeability from the topical solution, it has drawbacks such as the greater concentration of the drug required to produce the therapeutic effect. Also, the drug solution can simply wipe out from the nail surface after application. Hence, there is a necessary for a drug delivery system that overcomes the problems associated with the existing conventional topical solution formulation along with nail permeability improvement and residence time on the nail surface. In the recent era, colloidal based drug delivery has procured enormous importance in onychomycosis treatment due to its higher efficacy with fewer side effects. By formulating Efinaconazole into a colloidal based drug delivery system, it is possible to decrease the drug concentration into the formulation in comparison to existing conventional topical solution formulation as well as to enhance the nail permeability of Efinaconazole. The colloidal-based drug delivery systems include nanoparticles, microemulsions, nano emulsions, nano capsules, nanovesicles, transferosomes, liposomes, and hydrogel systems. Among all these drug delivery systems, the microemulsions based drug delivery has proven to be a thermodynamically stable and clinically beneficial system because of its versatileness, biocompatibility, ability to penetrate a drug molecule to deep layers of nail unit due to unique hydration properties of microemulsion ingredients as well as the longer shelf life of formulation.[3]

Essential oils are prescribed for a variety of health issues by traditional systems of medicine, all over the world. Various pharmaceutical and biological activities like, antibacterial, antifungal, anticancer, antimutagenic, antidiabetic, antiviral, anti-inflammatory etc., Because of the antifungal properties showed by essential oils, the aromatherapy has been used for treatment of serious skin diseases.[4] Hence, in the present work an attempt to study the antifungal effect of Efinaconazole along with (essential oil) Tea tree oil to be formulated as microemulsion and explore the synergetic antifungal effect.

II. MATERIALS AND METHODS:

Materials: Efinaconazole was gifted by (MSN Laboratories, Hyderabad India). Tween20, Tween80(Thomas baker PVT LTD, Mumbai),propylene glycoland methanol (S D Fine chemicals Mumbai), Carbopol 934(Central drug house, new Delhi), Eucalyptus citrodora oil purchased from (Swastik eucalyptus oil. Co., Ooty), tea tree oil purchased from (Heilen bio pharm, Gujarat).

Methods:

Solubility studies of Efinaconazole:

Solubility determination in the different oils, surfactants and co-surfactants for formulating micro emulsion drug delivery system. The solubility of the drug in various oils is an essential step for the micro emulsion formulation. So before starting the phase diagram one must have to choose the oil, surfactant and co-surfactant in which the drug shows maximum solubility, to be in the desired solubility range, which is required for the formulation of micro emulsion drug delivery system. Drug powder of Efinaconazole was added in excess to each of the oils, surfactants (S), cosurfactants (CoS) and then vortexed for mixing. After vertexing the samples were kept for 72 hours at ambient temperature for attaining equilibrium. The equilibrated samples were then centrifuged at 5000 rpm for 30 minutes to separate the undissolved drug. the supernatant was taken and diluted with methanol and observed by UV spectrophotometric method at 262nm. [5].

Construction of Pseudoternary phase diagram:

To find out the existence range of microemulsions, pseudo ternary phase diagrams were constructed by utilizing water titration method at ambient temperature (25 ºC). Based upon on the available solubility profile of the drug, Tea tree oil was selected as an oil phase, Tween20 and propylene glycol were used as surfactant and co-surfactant respectively. The Smix (surfactant+Co-surfactant) ratios were selected to be 1:1, 2:1 and 3:1 w/w and used. For each phase diagram at specific Smix concentration the Tea tree oil was added from the range of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1(%w/w) and the mixture were diluted with distilled water by sequential addition of 0.1ml of water using a micropipette. Water was added drop by drop while blending on a magnetic stirrer at room temperature, and the samples were marked as being visually clear or turbid. The microemulsion regions were recognized as transparent and isotropic mixtures. The percentage of three different phases, that is oil, water, and the mixture of surfactant and co-surfactant were calculated (Table 2). From the endpoint compositions of titrated samples, the mass percent composition of the components like oil, Smix and water was calculated and then plotted on

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ternaryplot.com to construct the pseudo ternary phase diagram.[6].

Preparation of Efinaconazole loaded microemulsion: Dissolve the drug in oil and then add surfactant and co-surfactant in fixed ratios and vertex the mixture for 15minutes continuously. Then add require quantity of water dropwise drop with stirring and allow to forming a clear transparent liquid, it shows formation of a microemulsion. Finally, the prepared microemulsions formulation incorporated to 1%w/w Carbopol 934 gel base.[7]

Evaluation of Efinaconazole microemulsion.[8-13]

1. Percenttransmittance:

The transparency of the microemulsion was determined by measuring the percentage transmittance at 650nm against distilled water as blank by using UV spectrophotometer (UV 1800, Shimadzu, Japan).

%T= Antilog (2-Absorbance)

2. pH and Viscositymeasurements:

The Rheological behaviour of the microemulsion formulation was evaluated using an Ostwald viscometer at a room temperature. The pH of Efinaconazole microemulsion formulations was determined by using digital pH meter. The measurement of pH of each formulation was done in triplicate and standard values were calculated.

3. %Drugcontent:

For the determination of drug content about one ml of each microemulsion formulationwas transfer to a 10 ml volumetric flask and dissolved in methanol. It was diluted appropriately and analyzed spectrophotometrically at 262 nm.

4. Measurementofglobule sizeand zetapotential:

The average globule size and zeta potential of the optimized microemulsions were measured using a Malvern Zeta seizer instrument at a temperature 25 °C.

5. Surfacemorphology:

Surface morphology of the optimized microemulsion formulations TTM3 will be determined by using a scanning electron microscope (SEM).

6. Centrifugation test:

The optimized microemulsion formulation TTM3 was centrifuged at 3500 rpm for 30 min to ensure physical stability.

7. Invitrodiffusionstudy:

In in-vitro diffusion study, the diffusion medium used was phosphate buffer pH 7.4. Assembly of diffusion cell for in-vitro diffusion studies the diffusion cell was planned as per the dimension given. Diffusion cell with an effective diffusion area of 3.14 cm2 was used for in-vitro permeation studies. The diffusion cells were deposited on the magnetic stirrers. The donor compartment consisting of 1 gm of microemulsion containing Efinaconazole. The receptor compartment was filled with fluid. Then the egg membrane was mounted on the cell carefully so as to avoid the entrapment of air bubble under the egg membrane. Intimate contact of egg membrane was ensured with receptor fluid by placing it tightly with clamp. The speed of the stirring was kept constant all over the experiment. With the help of 1ml pipette 1 ml of sample was withdrawn at a time interval of 60 min from sampling port of receptor compartment and same volume was the replaced with receptor fluid solution in order to continue sink condition. The samples were appropriately diluted and the absorbance was measured at 262 nm using UV spectrophotometer.

Evaluation of prepared microemulsion gel[14-18]

1. Spreadability:

Spreadability was performed by using two glass slides of length 7.5 cm. 350 mg of Microemulgel was weighed exactly and it was taken on one glass slide. one more glass slide was placed above it from a height of 5 cm. A weight of 5 gm was kept on the upper slide and after 1 min, diameter of circle that was spread was noted in cm. The detected diameter indicates the type of gel.

2. Viscosity and rheological studies:

Brookfield digital viscometer was used for the determination of viscosity and rheological properties of microemulsion based gel. The viscosity of gel was measured at discrete angular velocities at a temperature of 25 °C.

3. Determination of pH:

The apparent pH of the gel was determined by pH meter in triplicate at 25±1ºC.

4. Determination of % drug content:

For the determination of drug content 1 gm of gel formulation as weighed in 10 ml volumetric flask and dissolved in methanol. It was diluted

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appropriately and analyzed spectrophotometrically at 262 nm.

5. Invitrodrug release studies:

An invitro drug release study was performed using diffusion cell. Egg membrane was laydown between receptor and donor compartments. Microemulsion gel equivalent to 0.2gm was placed in the donor compartment and the receptor compartment was filled with phosphate buffer pH 7.4. The diffusion cells were maintained at 37 ± 0.5℃ with stirring at 100 rpm throughout the experiment. At fixed time interval, 5ml of sample was withdrawn for every 1,2,3,4,5 and 6 hrs. and same volume was replaced with receptor fluid solution in order to continue sink condition. The collected samples were analyzed by UV spectrophotometer at λ max 262nm.

6. Stability studies:

The prepared gel (TTM3) was subjected to stability study for a period ofthree months at room temperature.

7. In vitro antifungal activity studies:

Sterile Sabourd Dextrose Agar plates were prepared, by pouring the sterile agar into sterile Petri dishes under aseptic conditions. 0.1 ml of the test organism (Trichophyton rubrum) was spread on agar plates. 5 mm diameter holes were made in the agar plates using a sterile bore. 500µg/ml drug, 10µl of formulation TTM3, 10µl of essential oils (TTO) and 20mg of gels (TTM3-G) were added into each hole separately. The plates were maintained at +4˚C for 4 hrs to allow the diffusion of solution into the agar medium. All the plate-containing Trichophyton rubrum were incubated at 28˚C for 48 hrs. zones of inhibition of microbial growth around the well were measured and recorded after the incubation time.

III. RESULTS AND DISCUSSIONS

Microemulsion components screening according to solubility study

Based on the Efinaconazole solubility study data, the oil, surfactant, and co-surfactant components were selected in the present research work. Efinaconazole has shown the highest solubility in eucalyptus citrodora oil (154.56±6.32 mg/mL), methanol (136.21±5.06 mg/mL) and Tea tree oil (143.49±1.91 mg/mL) components among thevarious oils, surfactants and co-surfactants. Table 1 summarizes the solubility data for Efinaconazole by UV method.

Construction of Pseudoternary phase diagrams

The pseudo ternary stage charts of different proportions of surfactants (Tween 20) Co-surfactant (Propylene glycol) were utilized to develop. The Smix weight proportions [1:1, 2:1, 3:1] are addressed in Fig.1 and Table 2, in pseudo-ternary stage graph where microemulsion regions are noticed by using Ternary plot.com software.

Table 1. solubility profile of Efinaconazole

Phasetype	Excipient	Solubilitymg/ml
Aqueous	Water	0.259±0.015
Organicsolvent	Methanol	136.21±5.06
Oils	Tea tree oil	143.49±1.91
	Eucalyptus citrodora oil	154.56±6.32
	Thyme oil	134.34±1.16
Surfactants	Tween20	21.37±0.333
	Tween80	4.24±0.190
Co-Surfactants	Propylene glycol	8.96±0.271

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	Poly ethylene glycol 400	7.89±0.063
Phosphatebuffers	pH 6.8	0.133±0.019
	pH 7.4	0.370±0.036

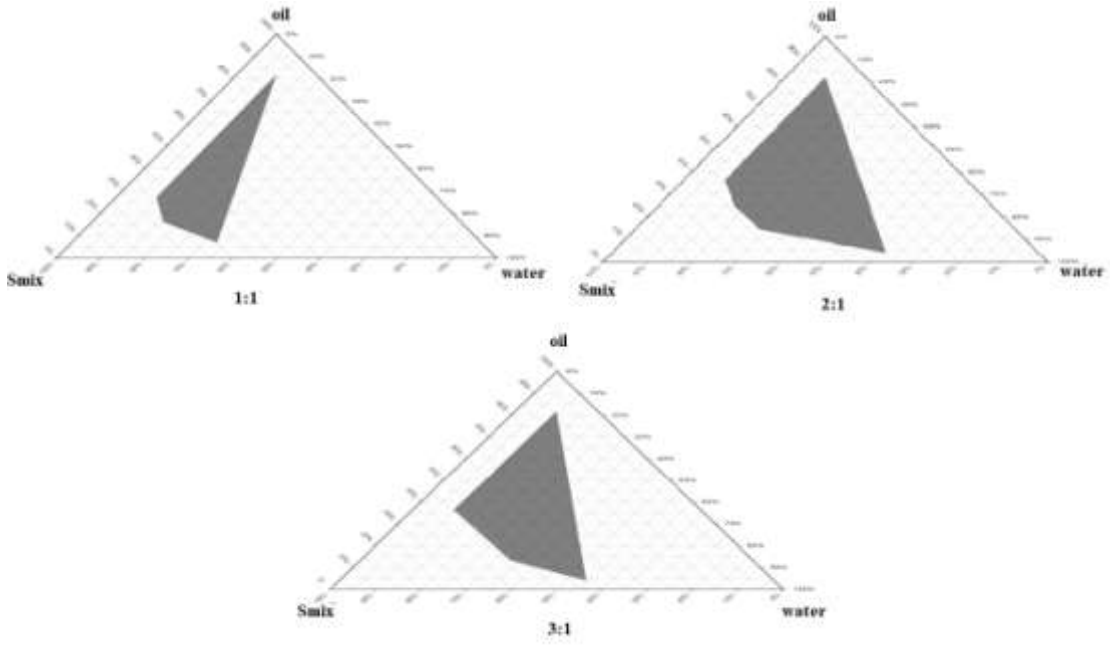

Fig 01: Pseudoternary phase diagram of tea tree oil, Tween 20, propylene glycol contains different Smix ratio (1:1, 2:1 and 3:1).

Table 2: Formulation development of Efinaconazole microemulsion with selected oil, Smix, water from the Pseudoternary phase

Formulation code	Smix ratio	Surfactant	Oils	Percent w/w component in formulation			
				Oil %	Smix %	Water%	Drug %
TTM1	1:1	Tween20	Tea tree oil	16	64	20	5
TTM2	2:1			30	54	15	5
TTM3	3:1			37	50	13	5

Evaluation of microemulsion

- **% Transmittance:**Clarity of microemulsion was checked by % transmittance. The transmittance values of all formulations are above 90% as shown in Table 3. The TTM3 formulation showed 99.46±0.132 compare to other formulations. which indicates that the microemulsions were clear and transparent in nature also indicates the globules in the formulation is in the nanometer range.
- **pH and viscosity measurements:**The pH of all the formulations is found in the range of 5.98 to 6.61 as shown in Table 3. This is well between the range for topical administered formulation. Formulation of TTM3 has shown pH 6.45±0.012. Therefore, there is no need for

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adjusting the pH of the formulation. The viscosity of microemulsion formulation was determined as shown in Table 3, all samples exhibited Newtonian flow behaviour and formulation TTM3 showed 12.84±0.48 cps shows less viscous compared to other microemulsion formulations.

- **Drug content:**The drug content of all the formulations of Efinaconazole microemulsion is shown in Table 3. TTM3 was exhibited 96.44±0.77% higher drug content than other formulations. The microemulsion drug content of all formulations was found to be within the range of 85-99% which was within the limits of USP specifications. it indicates uniformity in drug content without any degradation.

Table 3: Evaluation of Efinaconazole microemulsion formulation TTM1-TTM3

Formulation code	Transmittance	Viscosity cps	pH	%Drug content
TTM1	92.53±0.678	15.68±0.572	6.06±0.104	94.27±0.26
TTM2	97.56±0.132	16.70±0.582	6.35±0.073	90.00±0.14
TTM3	99.46±0.13	12.84±0.480	6.45±0.012	96.44±0.77

Measurementofglobule sizeand zetapotential: Theglobule size and zeta potential were measured by a Malvern zeta analyzer and it was Found that 250.3nm for TTM3(Fig 2). Confirmed that ME are within the required size ranges. The Zeta potential of microemulsion TTM3 was found to be -11.07 Mv (Fig 3) which indicates that the globules aggregation is not expected to take place so, they are sufficient to be stable.

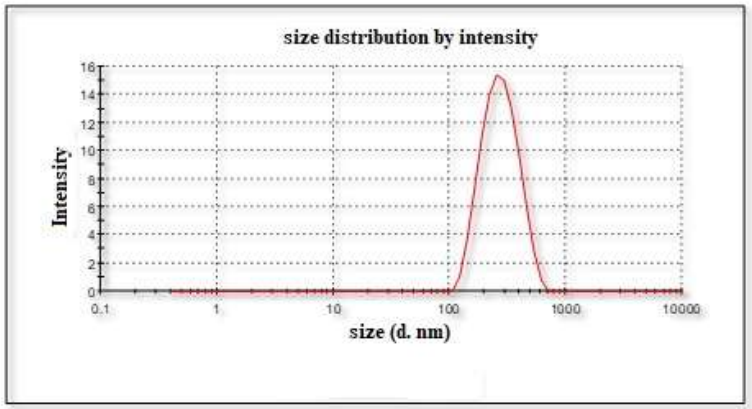

Fig 02: globule size of TTM-3

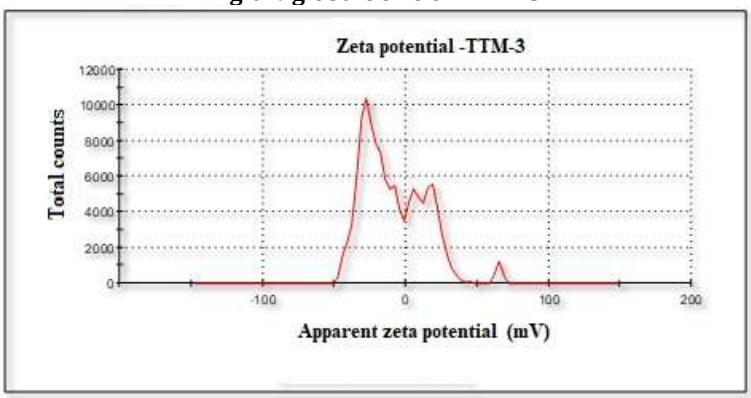

Fig 03: Zeta potential of TTM-3

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- **Surfacemorphology:**The surface morphology was studied by SEM for the optimized formulations which were confirmed that the drug is completely dissolved. This can have the ability to form a microemulsion. And the particles are globular with globule size in the nanometre scale with a smooth surface as shown in Figure 4, for TTM3.

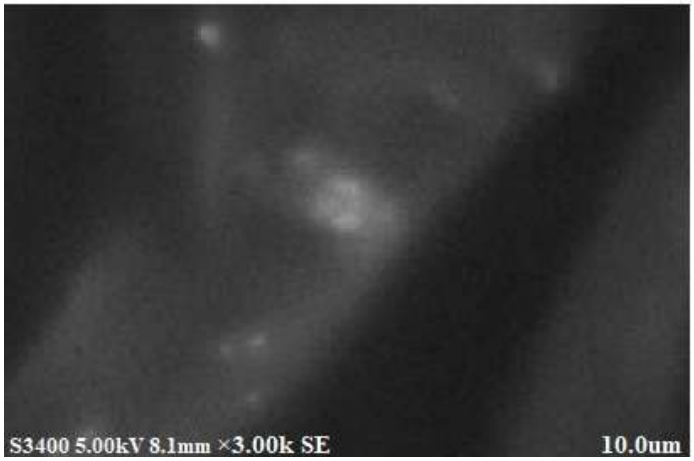

Fig 04: SEM image of TTM3

- **Centrifugation test:** There is no phase separation of optimized microemulsion formulation. consequently, TTM3 formulation will be monophasic in nature.
- **Invitrodiffusionstudy:** From the in vitro release studies, we observed that 0 - 20% of the drug was delivered in 1hrs and over half drug released in 3 hrs, and more than 80% of the drug released in 6 hrs. The formulation of TTM3 showed 93.33% (Figure 5). And it has shown a higher % of drug release when compared with other formulation. (Table 4).

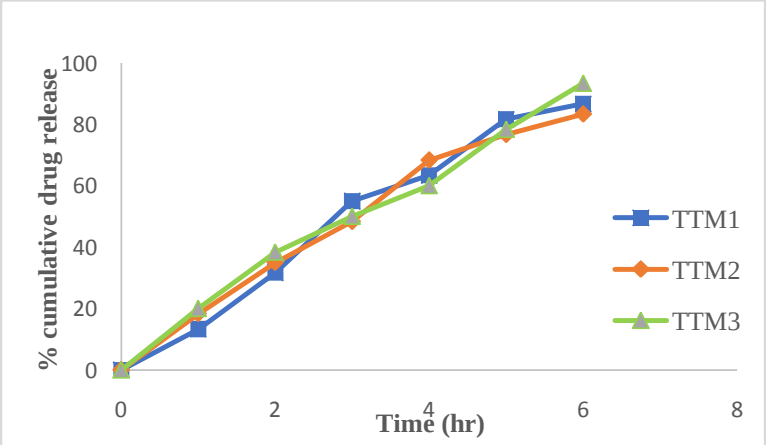

Fig 05: comparison of % cumulative drug release of TTM1-TTM3

Table 4. Invitro diffusion study of Tea tree oil microemulsion

Time in hrs	%CDR		
	TTM1	**TTM2**	**TTM3**
0	**0**	**0**	**0**
1	13.33	18.33	20.00
2	31.66	35.00	38.33
3	55.00	48.33	50.00
4	63.33	68.33	60.00
5	81.66	76.66	78.33
6	86.66	83.33	93.33

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Evaluation of microemulsion based gel

- **Spreadability:**The spreadability is an important property of topical formulation from a patient compliance point of view. The increase in the diameter due to spreading of the formulation gel TTM3-G1 was found to be 2.43± 0124cm.
- **Viscosity determination:** The microemulsion gelformulation TTM3-G1 showed 12050 ± 40.83cps. this value indicatesprobable retention of drug formulation on nail affected surface area without any drainage.
- **pH measurement:** The pH of microemulsion gel TTM3-G1 was found to be 6.59 ±0.07 (Table 5) and is suitable for topical application with minimum discomfort**.**
- **% Drug content:** The prepared Efinaconazole microemulsion gel TTM3-G1 subjected to drug content uniformity. The microemulsion gel was in the permissible range from 93.58 % respectively which indicated the drug uniformly dispersed throughout the formulation.

Table 5: Evaluation of microemulsion gel-based gel

Formulation code	Spreadability	Viscosity	pH	% Drug content
TTM3-G1	2.43± 0.12	12050 ± 40.83	6.59 ±0.07	93.58 ± 0.44

- **Invitro Drug release:** The result of the in-vitro release of Efinaconazole from the gel formulation. However, the results clearly show that the gels can retain the drug forprolonged periods. The % CDR ofmicroemulsion gel formulation TTM3-G1 was found to be 91.66% as shown in Figures 6.

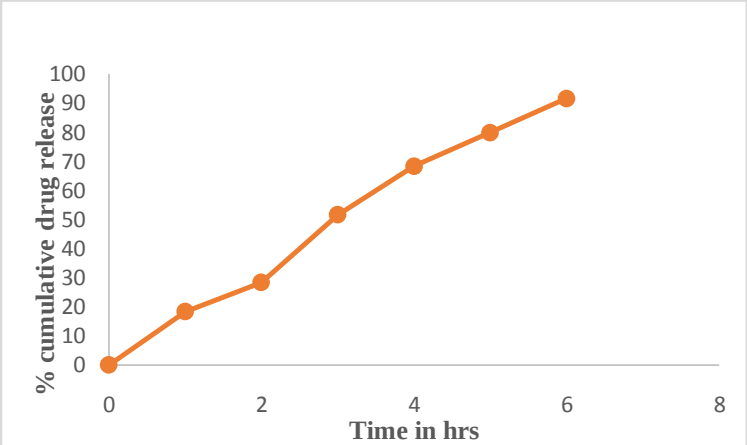

Fig 06: In-vitro drug release of TTM3-gel

- **Release kinetics studies**:The cumulative amount of drug released from all Efinaconazole microemulsionand microemulsion based gel formulations at different time interval was fitted to discrete models to find out the mechanism of drug release. The correlation coefficients table 6 showed that the kinetic of drug release from microemulsion (TTM1-TTM3)(fig: 7- fig11). and (TTM3-G) microemulsion based gel fallowed zero order model of kinetics(fig:8). 'n' values were found to be more than 0.5 this shows that the release approximates non-Fickian diffusion mechanism.

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Table 06: Release kinetics of optimized microemulsion and microemulsion based gel

Formulation code	Zero order	First order	Higuchi model	Peppas model	n values
	R^2	R^2	R^2	R^2	
TTM1	0.9805	0.9635	0.9233	0.7218	1.845
TTM2	0.9799	0.983	0.9485	0.6558	1.725
TTM3	0.9917	0.8668	0.9401	0.6405	1.711
TTM3-G	0.9905	0.9312	0.9208	0.6816	0.1779

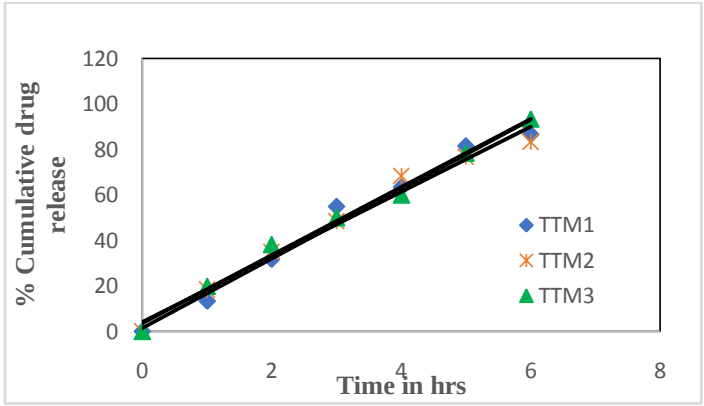

Figure 07: Zero order release kinetic profile of TTM1-TTM3

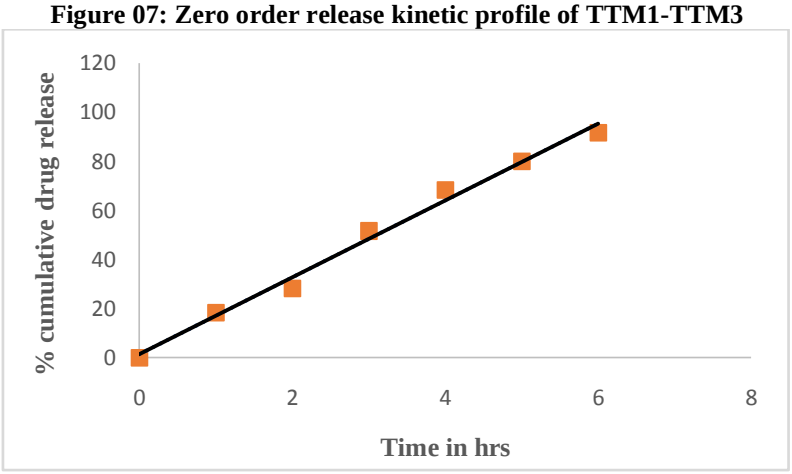

Figure 08: Zero order release kinetic profile of TTM3-G

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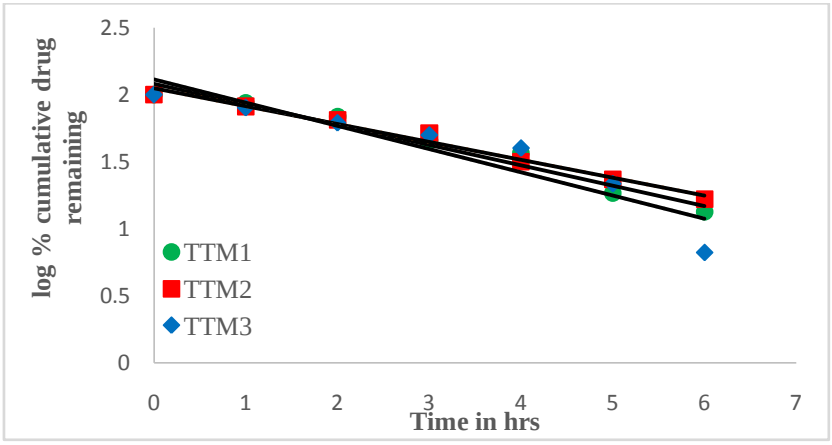

Figure 09: First order release kinetic profile of TTM1-TTM3

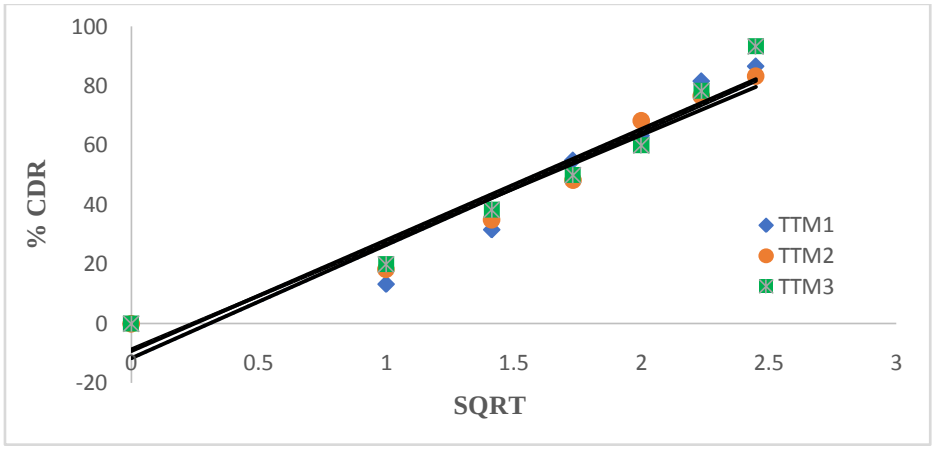

Figure10: Higuchi release kinetic profile of TTM1-TTM3

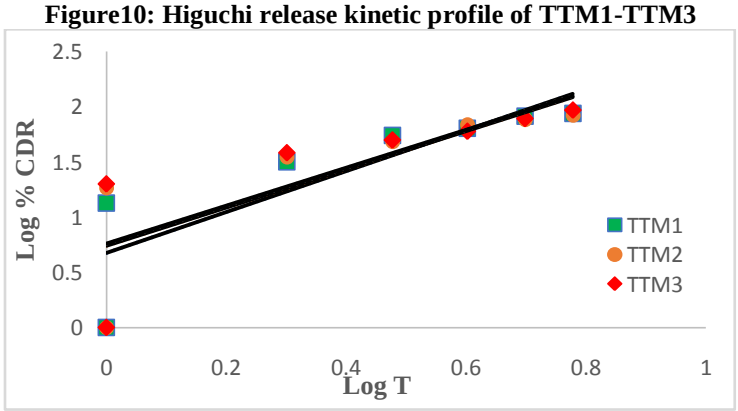

Figure11: peppas release kinetic profile of TTM1-TTM3

- **Invitro antifungal activity studies:**The in-vitro antifungal effect of optimized microemulsion formulations, Tea tree oil, and the drug has done against using fungal strain Trichophyton rubrum. The zone of inhibition was measured in terms of millimetres. The zone of inhibitions was measured 19mm for 500ug/ml of drug and 13mm for 10 µl of Tea tree oil, 24mm for TTM3, and 21mm for 20mg of TTM-3 gel. (Table 7) These microemulsion formulations have more effective in inhibiting the growth of Trichophyton rubrum fungal strain used in this study. (Fig:12) Optimized microemulsion and microemulsion gel (TTM3

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and TTM3-G) have a better antifungal effect than standard Drug, this proved that the synergistic effect could be achieved by Tea tree oil with Efinaconazole drug by microemulsion formulations.

Table 7: Report of antifungal activity against T. rubrum

Sl no	Samples	Quantity Used	Zone of inhibition in mm	Sensitivity
1.	Efinaconazole	500µg/ml	19	sensitive
2.	TTM-3	10µl	24	sensitive
4.	TTM-3 GEL	20mg	21	sensitive
6.	Tea tree oil	10µl	13	sensitive

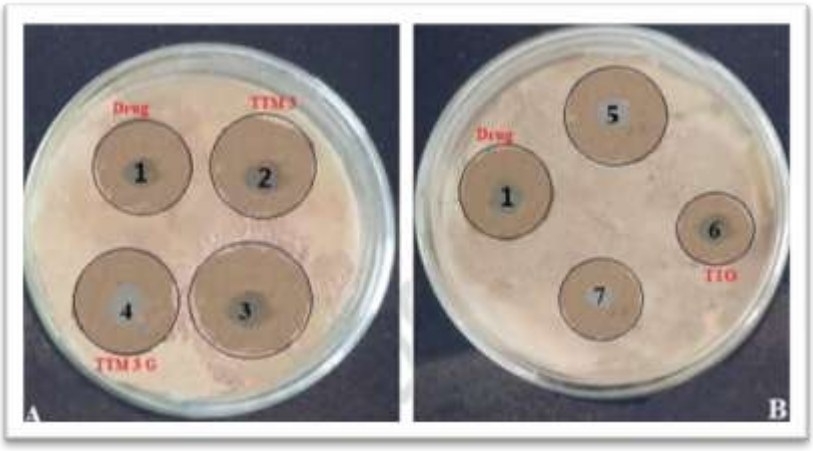

Figure 12: The antifungal activity against T. rubrum using agar well diffusion method.
A- Drug, TTM3, TTM3-G
B- Drug, Tea tree oil

- **Stability studies:** Stability studies of microemulsion gel formulation TTM3-G1 Shows that negligible change in drug content and % CDR revealed that the formulations are stable on storage.

IV. CONCLUSION:

The present study was aimed formulate and evaluate theEfinaconazole microemulsions with tea tree oil successfully. The optimized formulation (TTM3) shows %transmittance (99.46±0.13), pH(6.45±0.012),drug content (96.44±0.77), less viscous (12.84±0.480cps), invitro release (93.33%).and the optimized formulation converted into gel and it shows good spreadability, pH (6.59 ±0.07), drug content, invitro release and high viscosity (12,050cps) it indicates that drug retain for a prolong period of time on surface of nail or nail bed. The antifungal activity of optimized microemulsion and its gel shows more antifungal activity compare to drug and tea tree oil individually. So, successfully we achieved the synergistic effect of drug and tea tree oil in the form of microemulsions. The results showed that a microemulsion and Microemulgel formulationswere a promising dosage forms for topical administration of Efinaconazole.

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