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FORMULATION AND EVALUATION OF TOPICAL MICROEMULGEL LOADED WITH TERBINAFINE HCL MICROEMULSION

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Keywords:

Microemulgel, Topical delivery, Terbinafine hydrochloride, Micro-emulsion, Pseudo-ternary phase diagram, Propylene glycol, Tween 80, Polyethylene glycol 400,Carbopol 934, Hydroxy-propylmethyl cellulose

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ABSTRACT: The aim of the present study was to investigate the potential of a micro-emulgel formulation for topical delivery of Terbinafine. Terbinafine showed highest solubility in propylene glycol among the available oil phase. Tween 80 and polyethylene glycol 400 were used as surfactant and co-surfactant respectively. Using pseudo-ternary phase diagram 1:2 ratio of surfactant: co-surfactant was selected. Using Central Composite Design thirteen formulations with varying ranges of S_{mix} and oil phase were prepared. Final formulation was selected on the basis of transmittance. From optimization plot it was concluded that 27.93% of S_{mix} and 6.51% of oil phase gave maximum transmittance. Then, optimized formulation was used to prepare final microemulgel of terbinafine. Thirteen gel formulation from varying concentration of carbopol 934 and hydroxypropylmethyl cellulose was prepared and evaluated for extrudability, spread ability, drug content, *in-vitro* drug release, rheological study and *in-vitro* antifungal activity against Teniapedis. Formulations with suitable consistencies were selected and optimization was done on the basis of drug release and *ex-vivo* permeation study in goat skin. Formulation with 0.45gm of carbopol 934 and 0.3gm of HPMC showed better drug release and skin permeation than other formulations. This formulation was further compared with marketed terbinafine ointment and was found to give enhanced drug release and permeation.

INTRODUCTION: Topical drug delivery system avoids the first pass metabolism, gastrointestinal metabolic degradation and irritation associated with oral administration [1]. This drug delivery system is best for having local action on the skin related diseases [2]. Athlete's foot is one of those diseases with fungus *Tenia pedis* as a causative organism. Terbinafine Hydrochloride is an effective fungicidal agent against this organism and is widely used topically and orally [3].

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Terbinafine hydrochloride is a synthetic allylamine derivative which has been associated with serious life threatening events such as hepatic failure, severe cutaneous reaction and severe neutropenia when given orally [3, 4]. To overcome these problems topical delivery in the form of ointments and creams are available. Environmental degradation, instability, problem in drug absorption and less drug loading capacity of these conventional forms has led to formulation of novel drug delivery as gel [5]. Gel has better loading capacity, better stability, controlled release of incorporated drug, excellent biocompatibility, pleasant transparent appearance and ease of application. But despite all these advantages it presents problem for incorporating hydrophobic drugs like Terbinafine hydrochloride. To overcome this problem microemulgel is

devised[5]. Microemulgel is a gel consisting of microemulsion having droplet size ranging from 10 to 100 nm. Microemulsions are thermodynamically stable and can incorporate both hydrophillic and hydrophobic drugs. They are multi-component systems comprising non-polar, aqueous, surfactant and co-surfactant components. When surfactants are included in immiscible mixture of oil and water the surfactant molecule can locate at the oil/water interface and lower the surface tension of the interface. Most of the hydrophobic drugs cannot be incorporated directly into gel base because solubility acts as a barrier and problem arises during the release of the drug. Oil phase incorporates the hydrophobic drug which is then homogenously dispersed as fine dispersion in aqueous phase using the mixture of surfactant and co-surfactant which reduces the interfacial tension between two liquid phases and increases their miscibility [6, 7].

Formulating microemulgel has been the object of many studies. Devada *et al.*, Patel *et al.*, and Kamble *et al.*, worked on producing microemulsion based gel system of itraconazole using various oil phase, surfactant and co-surfactant [8]. Similarly, Haneefa *et al.*, devised a herbal microemulgel of *Pothos scandens* and studied the influence of the type of the gelling agent on the drug release using three types of gelling agent: Carbopol 934, carbopol 930 and HPMC K4M [9]. Microemulgel containing Terbinafine HCl were formulated by Chauhan *et al.*, using cinnamon oil as oil phase, Tween 80 as surfactant and isopropyl alcohol as co-surfactant [10]. Likewise, Dhabi *et al.*, used cottonseed oil as oil phase, Tween 80 as surfactant and ethanol as co-surfactant for formulating microemulgel of Terbinafine HCl [11]. Micro-emulsion based gel as a vehicle for transungual drug delivery of terbinafine hydrochloride for the treatment of onychomycosis devised by Thatai and Sapra exhibited that the microemulsion-based gel showed better penetration (~5 folds) as well as more retention (~9 fold) in the animal hoof as compared to the commercial cream [12].

Microemulgel with its micron sized globule has better penetration and with gelling property exhibits controlled drug release. Relative stability and ease of application and removal offered by gel system makes it sound topical drug delivery over other forms for hydrophobic drug like Terbinafine HCL [13].

MATERIAL AND METHODS: Terbinafine hydrochloride was obtained as a gift sample from Simca Pharmaceutical Pvt. Ltd., Bhaktapur. excipients were provided by Department of Pharmacy, Kathmandu University.

Screening of Excipients by Solubility Studies: Different oils including oleic acid, liquid paraffin, propylene glycol and various surfactants like tween 80 and tween 20 were screened for solubility studies. Excess amount of drug was added to different oils and surfactants. The mixture was continuously stirred in Rotary Shaker for 72 hour at room temperature and was subjected to centrifugation at 1000 rpm for 15 minutes. Supernatant liquid was decanted off and subjected to filtration using membrane filter. 1ml of filtrate was withdrawn and diluted with methanol to 1000 ml. The diluted samples were observed at 283 nm in UV-Vis spectrophotometer. The concentration of sample soluble in different oil and surfactant was measured comparing with standard calibration curve of Terbinafine HCL in methanol.

TABLE 1: SOLUBILITY OF TERBINAFINE HCL IN DIFFERENT OIL, SURFACTANT AND CO-SURFACTANT

Components	Solubility (mg/ml)
Propylene glycol	26.48
Liquid paraffin	0.73
Polyethylene glycol 400	20.98
Tween 80	9.53

Construction of Pseudo-ternary Phase Diagram: Propylene glycol was selected as oil phase from solubility studies. Tween 80 and polyethylene glycol were selected as surfactant and co surfactant respectively. Tween 80 was selected also on the basis of HLB value which is 15 and suitable for o/w formulation. Surfactant and co-surfactant were mixed (S_{mix}) in 1:2, 2:1, 3:1 and 4:1 ratios. Chemix software was used to generate pseudo-ternary phase diagram. For each phase diagram, oil and S_{mix} at a specific ratio were mixed thoroughly in vortex mixer to give oil: S_{mix} at different ratio from 9:1 to 1:9 in different glass vial. Each mixture was titrated with water and visual observation was made for transparent o/w microemulsion. End point for the titration was turbid appearance of mixture. From the findings of water titration method pseudo-

ternary phase diagram was constructed with one axis representing aqueous phase, the second one representing oil and third representing a mixture of surfactant and co-surfactant [14].

Preparation of Terbinafine Loaded Microemulsion: S_{mix} with 1:2 ratio of surfactant to co-surfactant was selected as this showed the greater region of emulsification. Thirteen formulations were generated having varying amount of S_{mix} and oil phase as obtained from pseudo-ternary phase diagram using central composite design from Minitab [16]. Surfactant co-surfactant mixture was added to oil phase and preservatives were added to aqueous phase. Then, both phases were heated separately to 60-70 °C. Oil phase was added to aqueous phase with continuous stirring using vortex mixture.

TABLE 2: CENTRAL COMPOSITE DESIGN FOR FORMULATION OF MICROEMULSION

Formulation	S_{mix} (gm)	Oil (gm)	Water (gm)
F1	16.8	2.4	20.8
F2	16	0.8	23.2
F3	10.8	2.4	26.8
F4	14	2.4	23.6
F5	14	2.4	23.6
F6	14	2.4	23.6
F7	14	2.4	23.6
F8	16	0.4	23.6
F9	14	0.1	25.9
F10	14	2.4	23.6
F11	12	0.8	27.2
F12	12	0.4	27.6
F13	14	4.6	21.4

Characterisation of Microemulsion:

Percentage Trasmittance and Viscosity: The percentage transmittance of different batches was measured at 283 nm against distilled water as a blank in UV- spectrophotometer. The viscosity was measured by Brookfield Viscometer DV – III ultra using Spindle number 62 at 200 RPM.

Drug Content: The drug content was determined by dissolving 1gm of the formulation equivalent to 20mg of active drug in 100ml of phosphate buffer. It was further subjected to 100 times dilution. After suitable dilution with phosphate buffer, the absorbance was measured at 283 nm.

Drug Release: An accurately measured amount of microemulsion formulation equivalent to 20mg was introduced in a cellophane bag and was kept in an eight stage dissolution test apparatus containing 1000ml of phosphate buffer pH 5.8. The temperature was set to 37 ± 0.5 °C and the RPM was set to 50. Aliquots of 5ml of the medium were withdrawn every 30 min and replaced with fresh phosphate buffer. The absorbance of the sample was measured by using UV-Visible Spectrophotometer at 283nm.

Percentage transmittance was used as a response to optimise the amount of S_{mix} and oil to get desired microemulsion. Obtained formulation was then incorporated into the gel.

Preparation of Terbinafine Loaded Microemulgel: Carbopol 934 and HPMC were used to prepare the gel. These two were selected as independent variable to get thirteen formulations of gel using central composite design (**Table 3**). Total weight of the gel was kept 30 gm. Gelling agents were suspended in water and hydrated for overnight. The pH was adjusted around 6 to 6.5 using triethanolamine. Microemulsion was then incorporated in different formulations of gel in the ratio of 1:2 with continuous stirring.

TABLE 3: CENTRAL COMPOSITE DESIGN FOR FORMULATION OF GEL

Formulation	Carbopol 934 (gm)	HPMC (gm)	Water (gm)
G1	0.45	0.30	29.25
G2	0.30	0.60	29.1
G3	0.09	0.60	29.31
G4	0.15	0.90	28.95
G5	0.15	0.90	28.95
G6	0.15	0.90	28.95
G7	0.51	0.60	28.89
G8	0.15	0.30	29.55
G9	0.45	0.30	29.25
G10	0.45	0.30	29.25
G11	0.3	0.13	29.52
G12	0.3	1.02	28.67
G13	0.45	0.90	28.65

Characterization of Microemulgel:

Viscosity: Viscosity of the gels was determined using a Brookfield digital viscometer DV - III ultra using Spindle number 62 at 200 RPM.

Drug Content: The Terbinafine hydrochloride gel equivalent to 20mg drug was dissolved in 100ml of water. 1ml of solution was withdrawn and volume was made up to 100ml. The absorbance was measured after suitable dilution at 283nm against

the corresponding blank solution by using UV Spectrophotometer (UV-1700, Shimadzu).

Spreadability: 0.5gm of microemulgel was placed within circle of 1cm diameter pre-marked on a glass plate, over which second plate is placed. A weight of 500g was allowed to rest on the upper glass plate for 5 min. The increase in diameter was noted.

Extrudability: Extrudability was calculated by filling aluminum tube with 15gm of gel. The consistency of gel was observed on pressing the tube applying mild force.

***Ex vivo* Permeation:** Modified Franz diffusion cell was used for this study. Skin of goat was used for the skin permeation study. The skin was mounted in modified Franz diffusion cell and known quantity (0.5gm gel containing 10mg of drug) was spread uniformly on the skin on donor side. pH 5.8 phosphate buffer was used as the acceptor medium, from which samples were collected at regular interval for 12 hour and replaced with the same amount of buffer to maintain the receptor phase volume to 250ml. absorbance was measured at 283nm using UV-Spectrophotometer and the concentration was calculated using the equation of the calibration curve.

***In vitro* Release Study:** Release study profile of gel was studied using USP apparatus I. Cellophane membrane was used and weighed quantity of gel containing 10mg of drug was introduced in the membrane and clipped on the both sides. This was then dipped in basket containing 5.8 pH buffer as dissolution medium. The speed of the rotation was 50 rpm and temperature was maintained at 37 ± 0.5 °C [14]. Sample aliquots were withdrawn from dissolution medium at predetermined time intervals and were analyzed by UV-Spectrophotometer at 283nm. The concentration was calculated using the equation of calibration curve [15].

Antifungal Property: 20gm of Dermatophyte agar media was dissolved in sterile distilled water and then sterilized in the autoclave. Five petri plates wrapped with aluminium foil were sterilized by dry heat in hot air oven (Temperature 160 °C for 2 hours). Strains of Tenia pedis was diluted with water to prepare the inoculums. The media was poured in sterilized petri dishes under aseptic condition and allowed the media to solidify. The media was inoculated with strains of microorganisms. About 0.5gm of test sample was loaded in the media with great care. The marketed ointment of terbinafine HCL was placed in the media. The distance of 3cm was maintained between marketed and formulated sample. The plates were allowed to stand for about half an hour till the test samples completely diffuses in the media. Then the plates were incubated at the temperature of 30 °C for 48 hours. After 48 hours, the zone of inhibition was measured with the help of measuring ruler [16].

RESULT AND DISCUSSION: Solubility studies of the drug in different solvents *viz.* propylene glycol, liquid paraffin, polyethylene glycol 400 and tween 80 showed that highest solubility of 26.48 mg /ml was evident in propylene glycol. Hence, it was selected as oil phase for formulation. Other solvents polyethylene glycol 400 and tween 80 also acted as better solvent for drug with solubility of 20.98 mg/ml and 9.53 mg/ml respectively. Tween 80 was selected as surfactant and Polyethylene glycol was selected as co-surfactant.

Among the ternary phase diagrams constructed using surfactant and co-surfactant in 1:2 (**Fig. 2**), 2:1 (**Fig. 1**), 3:1 (**Fig. 3**) and 4:1 ratios (**Fig. 4**), the one with 1:2 ratio exhibited largest area of microemulsion. This ratio of surfactant and co-surfactant was selected for microemulsion preparation. Concentration range of water, oil phase and S_{mix} was obtained from ternary phase diagram.

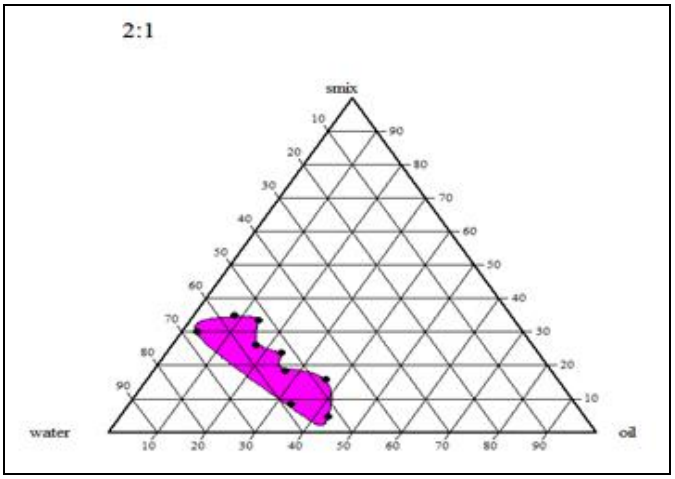

FIG. 1: PSEUDO TERNARY PHASE DIAGRAM OF WATER, OIL AND S_{MIX} (2:1)

These ranges were used to generate formulations by central composite design. These formulations were then characterized. Formulation F3 containing 10.8gm S_{mix}, 2.4gm oil and 26.8gm water showed greater transmittance and lowest viscosity compared to other formulations.

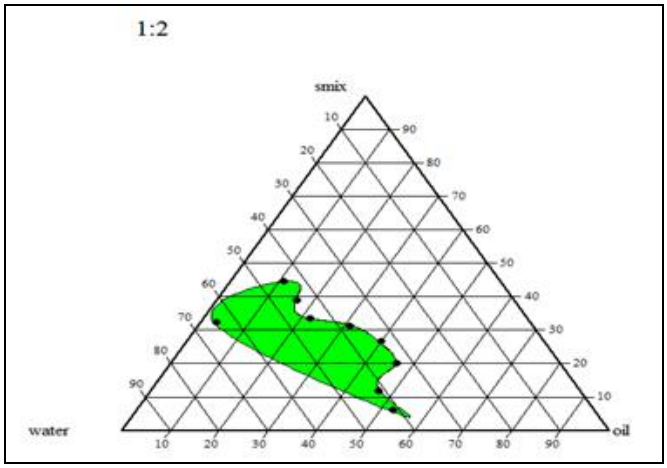

FIG. 2: PSEUDO TERNARY PHASE DIAGRAM OF WATER, OIL AND S_{MIX} (1:2)

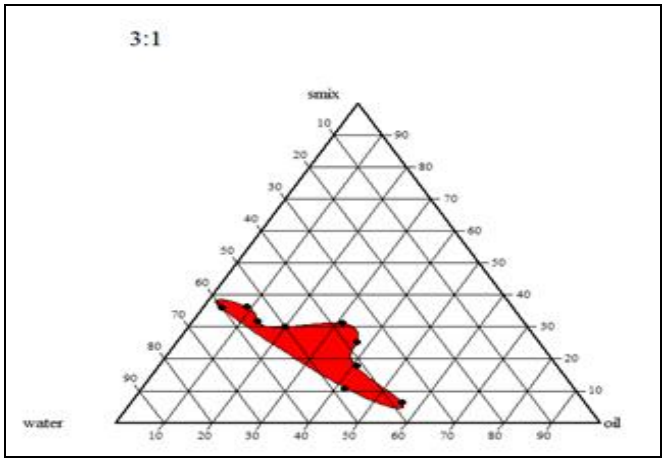

FIG. 3: PSEUDO TERNARY PHASE DIAGRAM OF WATER, OIL AND S_{MIX} (3:1)

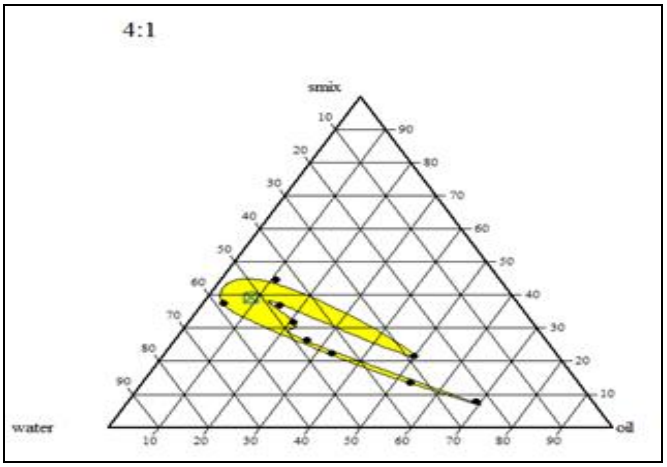

FIG. 4: PSEUDO TERNARY PHASE DIAGRAM OF WATER, OIL AND S_{MIX} (4:1)

Optimization of Microemulsion: The independent parameters selected for optimization were concentration of S_{mix} and oil and the dependent parameter was % transmittance. Surface plot indicates that the transmittance is high when S_{mix} is at lower concentration while formulation with oil phase at low and high concentration showed less transmittance than other formulations. This might be because at high concentration of S_{mix}, above the critical micelle concentration, they themselves form aggregates and lower the percentage transmittance. Oil phase needs to be in optimum concentration with respect to surfactant concentration. At lower concentration of S_{mix} both low and high concentration of oil phase showed higher tramsmittance than with high amount of S_{mix}. Formulation with highest transmittance was that with low S_{mix} and medium concentration of oil phase. Contour plot clearly showed that transmittance is higher when oil is between 4-8% and S_{mix} is below 30%.

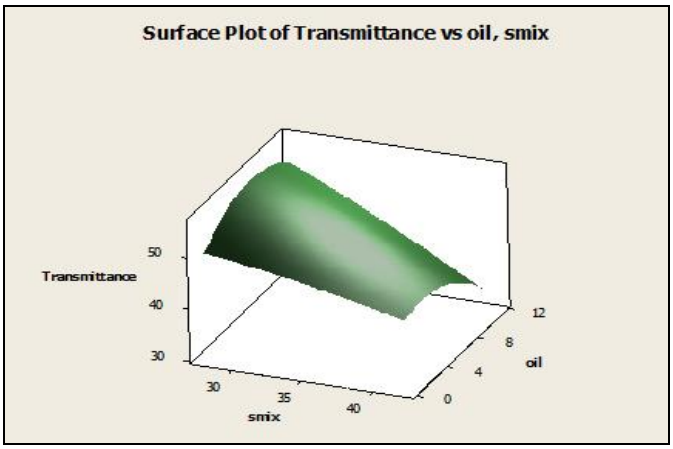

FIG. 5: SURFACE PLOT OF TRANSMITTANCE VS. OIL, S_{MIX}

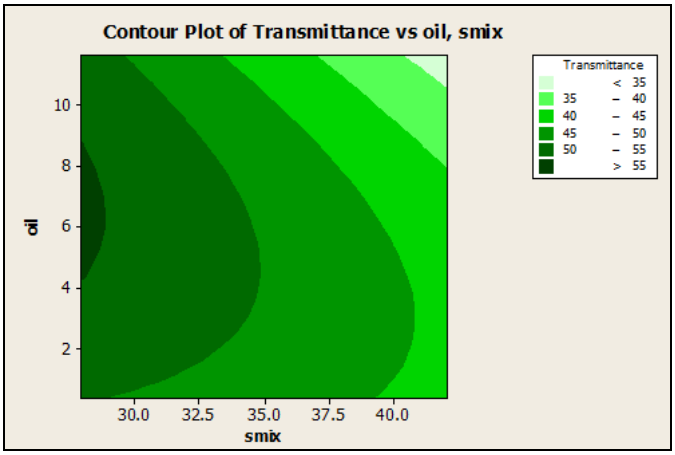

FIG. 6: CONTOUR PLOT OF TRANSMITTANCE VS. OIL, S_{MIX}

Optimization plot was developed using % transmittance as a dependent variable and % of S_{mix} and oil as independent variable. Depending upon the optimization plot the microemulsion was developed with S_{mix} concentration of 27.93% and oil concentration of 6.51%.

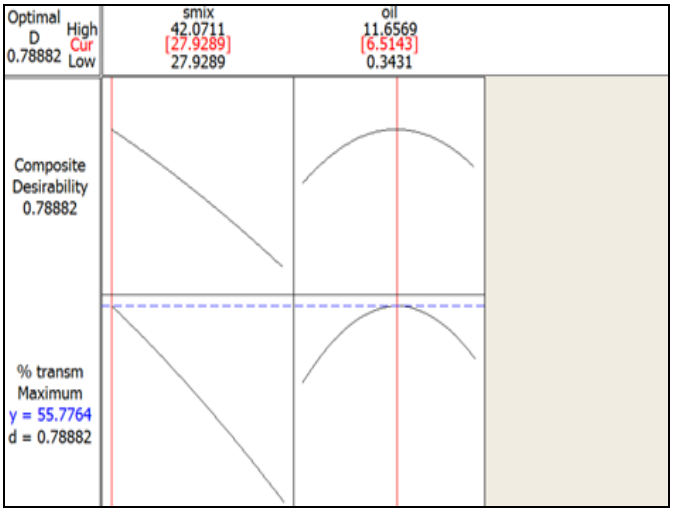

FIG. 7: OPTIMIZATION PLOT FOR MICROEMULSION

2% drug of total formulation was loaded in oil phase and microemulsion was prepared. Thus prepared formulation was evaluated for its following characteristics.

TABLE 4: CHARACTERIZATION OF OPTIMIZED MICROEMULSION

Characteristics	Results
Percentage transmittance	53.04 (nearer to that obtained from optimization plot)
Drug content	90.25%
Viscosity	16.91 cps
Conductivity	220 mv
pH value	3.1
Dilution test	Soluble with water as external phase
Centrifugation	No phase separation
Drug release	After 3 hours was 99.72 (*in vitro*) and 98.52 (*ex vivo*)

Characterization of Microemulgel: Optimized microemulsion was then incorporated in different formulations of gel in the ratio of 1:2 with continuous stirring to obtain microemulgel which were then characterized.

TABLE 5: CHARACTERIZATION OF MICROEMULGEL

Formulations	Spreadibility (cm)	% Torque	Viscosity (cps)	Drug content
MEG1	4.5	35.6	1067.77	87.5
MEG2	7.5	16.5	494.89	45.8
MEG3	7.5	0.25	7.497	43
MEG4	7.5	1	29.99	59.7
MEG5	7.5	1	29.99	11.94
MEG6	7.5	1	29.99	11.94
MEG7	7.5	1	29.99	11.94
MEG8	3.5	44.8	1343.7	16.38
MEG9	7.5	0.2	5.998	13.05
MEG10	7.5	1	29.99	11.94
MEG11	7.5	3.2	95.968	19.16
MEG12	4	17.2	515.828	14.72
MEG13	3.5	80.3	2408	13.61

TABLE 6: CUMULATIVE PERCENTAGE DRUG RELEASE OF FORMULATIONS WITH SUITABLE SPREADIBILITY

Formulation	Cumulative percentage drug release (*In vitro*)	Cumulative percentage drug release (*Ex vivo*)
MEG1	92.78	94.96
MEG5	68.97	73.79
MEG8	59.34	71.73
MEG9	77.14	68.88

Microemulsion loaded gel formulations were found to have varying consistencies. Except formulations MEG1, MEG5, MEG8 and MEG9 other preparations overflowed the glass slide showing liquid like property. Therefore microemulgels with better consistencies were selected on the basis of spreadability for further characterization. Drug release and permeation studies were performed on these batches to select best formulation. Cumulative percentage drug release both *in vitro* and *in vivo* was highest in formulation MEG1.

Comparison of Microemulgel with Marketed Terbinafine Ointment: Zone of inhibition of best formulated microemulgel MEG1 was larger than that of marketed terbinafine ointment. This might

be attributed to better permeation of drug into the surrounding area as it is dissolved into the micro droplets which diffused into the media with better ease than the normal marketed ointment.

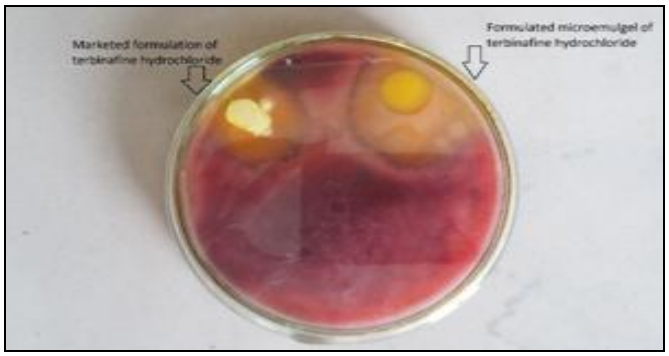

FIG. 8: ZONE OF INHIBITION OF MARKETED TERBINAFINE OINTMENT AND OPTIMIZED MICROEMULGEL

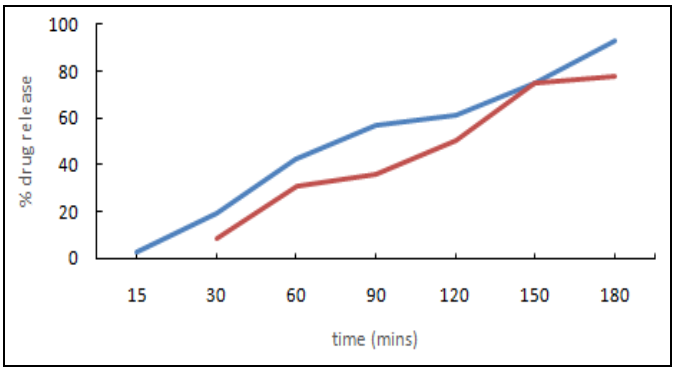

FIG. 9: *IN VITRO* DRUG RELEASE PROFILE OF MICROEMULSION AND MARKETED TERBINAFINE OINTMENT

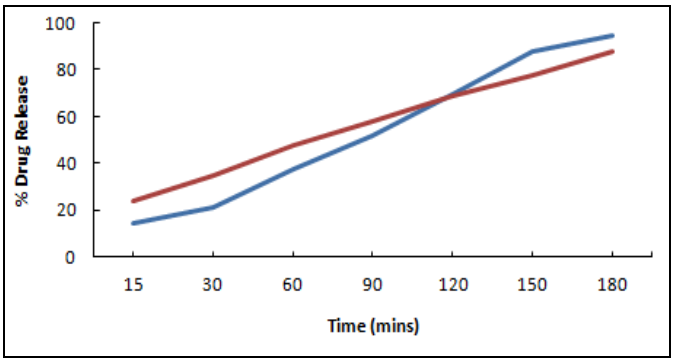

FIG. 10: *EX VIVO* DRUG RELEASE PROFILE OF MICROEMULSION AND MICROEMULGEL

This formulation also showed better drug release both *in vitro* and *ex vivo* than the marketed terbinafine ointment. From *in vitro* and *ex vivo* release profiles, dissolution behavior of terbinafine microemulgel (92.78% and 94.96% respectively) was seen to increase as compared to marketed product (78.15 and 87.84 respectively) which may be attributed to decrease in particle size and thus increase in solubility and bioavailability. Hence, the comparative study indicated that formulation MEG1 showed better drug release, better skin permeation, optimum viscosity and drug content.

Drug Release Kinetics: Drug release data of optimized formulations were fitted into three different mathematical models namely zero order, first order and Higuchi model. R^2 value for zero order, first order and Higuchi model were 0.98, 0.74 and 0.99 respectively. This suggests that drug release from microemulgel followed Higuchi model which suggests controlled release of drug. Drug diffuses from the surface in contact with the skin then more drug moves out to the emulgel matrix to maintain the constant drug amount available for the release.

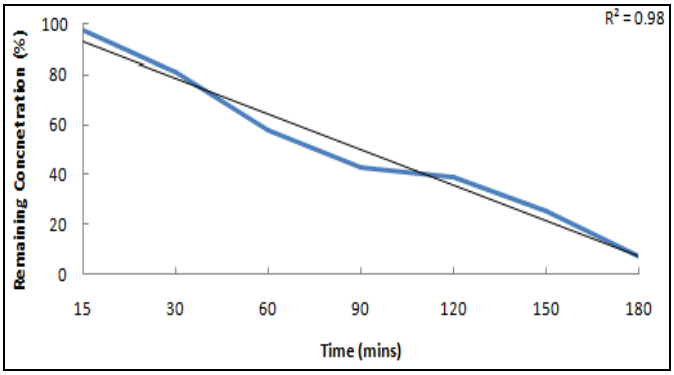

FIG. 11: ZERO ORDER MODEL

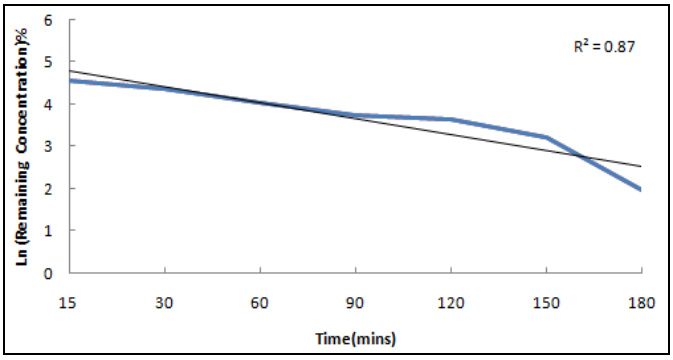

FIG. 12: FIRST ORDER MODEL

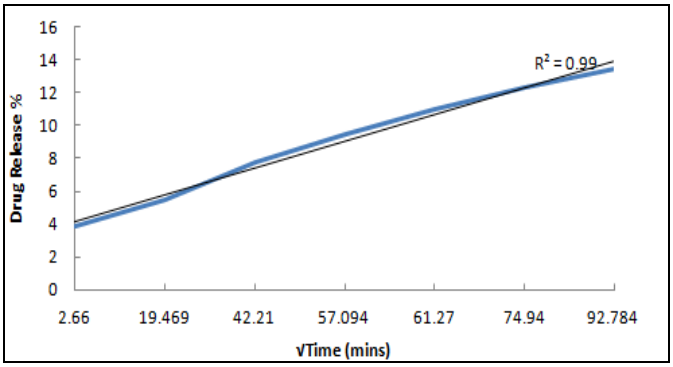

FIG. 13: HIGUCHI MODEL

CONCLUSION: The prime objective of present work was to develop a novel drug delivery system with enhanced therapeutic efficacy by improving the solubility, permeability and hence bioavailability of terbinafine using microemulgel. The present study revealed that spontaneous emulsification method can be used for preparation of micronized formulations. Optimized formulation of microemulgel was formulated and when it was characterized for physical appearance and drug release it appeared to be superior to marketed terbinafine ointent. From *in vitro* and *ex vivo* data, it can be concluded that the developed microemulsion have increased the bioavailability of a poorly water soluble drug, terbinafine. Thus, our study confirmed that the microemulgel formulation can be used for topical formulation of terbinafine.

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CONFLICT OF INTEREST: The authors declare that there is no conflict of interest.

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