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RESEARCH ARTICLE

FORMULATION AND CHARACTERIZATION OF TOPICAL NANO EMULGEL OF TERBINAFINE

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Abstract

Objective: Terbinafine is a broad spectrum antifungal drug. The aim of present study was to develop topical nano emulgel of terbinafine using carbopol 934 as a gelling agent. The objective behind the formulation was to avoid dosing frequency and to increase the stability and bioavailability by avoiding the first pass metabolism.
Methods: The formulations were prepared by using oleic acid, carbopol 934, span 20, propylene glycol in different ratios and analyzed by pseudo tertiary phase diagram. All the five prepared nano emulgel formulations have shown satisfactory physiochemical properties. The stability and particle size is been determined by zeta potential.
Results: The highest drug release 82.38 %was found in formulations of batch F4, which follows non-fickian mechanism. The studies showed that changing the concentration of oil, surfactant, co surfactant and double distilled water as aqueous phase has an impact on the behavior and thermodynamic stability of the nanoemulsion.
Conclusion: Study concludes that of Terbinafine can be delivered effectively by nano emulgel formulations.
Keywords: Antifungal drug, nano emulsion, nano emulgel, Terbinafine, topical drug delivery, tertiary phase.

INTRODUCTION

Nanoemulgel has emerged as one of the most interesting topical delivery system as it has dual release control system i.e. hydrogel and nanoemulsion. Nanoemulgel having nanosize (10 to 100 µm) rapidly penetrates and deliver active substance deeper and quicker. Gelling agent promotes better stability of nanoemulsion by reducing the surface and interfacial tension and also enhancing viscosity of the aqueous phase for drug administration topically[1,2]. Drug delivered through nanoemulgel has better adhesion on the surface on the surface of the skin and high solubilizing capacity which leads to larger concentration gradient towards the skin, hence influences better skin penetration. Nanoemulsions are thermodynamically stable, transparent, or translucent dispersion of two immiscible liquids, such as oil and water stabilized by an interfacial film of surfactant and cosurfactant molecules having the droplet size of less than 100 nm. It also retard dosing frequency of drug[3,4].
Terbinafine [(2E)-6,6-dimethylhept-2-en-4-yn-1yl] (methyl) (naphthalene-1-ylmethyl)amine is a broad spectrum antifungal drug active against dermatophytes. Dermatophytes cause infections of the skin, hair and nails, obtaining nutrients from keratinized material. Some of these skin infections are known as ringworm or tinea. Terbinafine has first pass effect due to this shows poor oral bioavailability. It inhibits ergoterol synthesis by inhibiting squalene epoxidase, an enzyme that is a part of fungal cell membrane synthesis pathway. Because terbinafine prevent conversion of squalene to lanosterol, ergosterol cannot be synthesized, and caused fungal cell lysis[5].
The objective of present study was to develop a most effective topical preparation to avoid first pass metabolism of drug, with enhanced pharmacological action on local area, enhanced penetration of drug with the help of penetration enhancer, improved and better drug release profile of the drug by preparing a suitable nanoemulgel for the treatment of fungal infection[6].

MATERIALS AND METHODS

Terbinafine was obtained from Yarrow chem. product Uttarakhand, India, Oleic acid, Span 20, propylene

glycol, Carbopol 934 were obtained from Molychem. pvt. Ltd. All other ingredients, chemicals and solvents used were of analytical grade.

Fourier Transform Infrared (FTIR) spectral analysis

IR analysis was done on IR spectrometer with KBr disc. In IR the spectrum was recorded in the wavelength region of 4000 to 400 cm^{-1}. Total 10 mg of drug was mixed with KBr and triturated then it was placed in holder and pressed to form a pellet. It was placed under IR beam and a spectrum was obtained on computer. The IR spectrum of drug exhibit maxima only at the same wavelength as that of similar preparation of the corresponding reference standard, thus IR spectrum of substance being examined should be concordant with the reference spectrum of the drug.

Solubility Study

Solubility of Terbinafine was determined in various oils such as oleic acid, isopropyl myristate, clove oil, castor oil and olive oil by shake flask method. An excess amount of drug was taken in 10 ml of the oil in vials, and mixed using vortex mixer. The vials were then kept at 25±1°C in an isothermal shaker. The samples were then centrifuged at 3,500 rpm for 15 min. The supernatant was filtered through whatman (no. 41) filter paper. The filtrate was suitably diluted. The amount of drug dissolved in the oil was determined using UV spectrophotometer at their respective wavelength[7].

Partition coefficient

It is a ratio of unionized drug distribution between organic and aqueous phase at equilibrium. It was determined in n- octanol: water system, by taking 25 ml of both n-octanol and water in separating funnel. Shake this mixture for 30 minutes and keep it for 24 hour. Then 10 mg drug mixed with saturated solution of n-octanol: water in separating funnel. The separating funnel was shaken for 24 hours. The two phases was separated and the amount of the drug in aqueous phase was analyzed by UV at 282.7 nm after appropriate dilution.

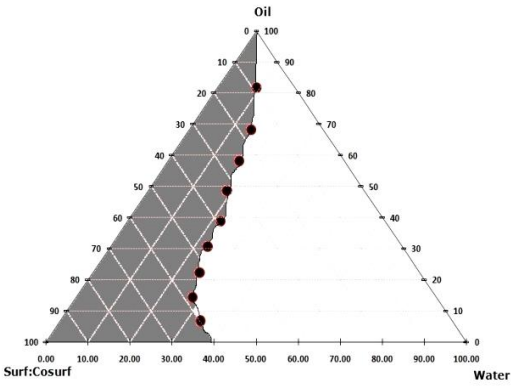

Figure 1: Pseudo-ternary phase diagram at 1:1 weight ratio of surf:cosurf .

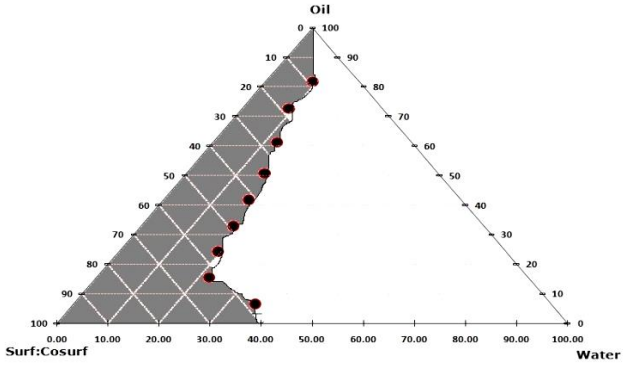

Figure 2: Pseudo-ternary phase diagram at 2:1 weight ratio of surf:cosurf.

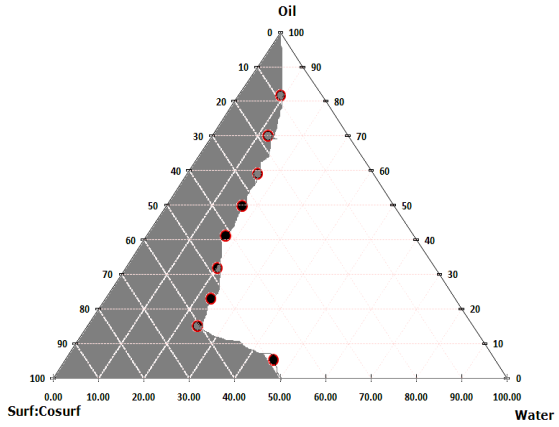

Figure 3: Pseudo-ternary phase diagram at 1:2 weight ratio of surf:cosurf.

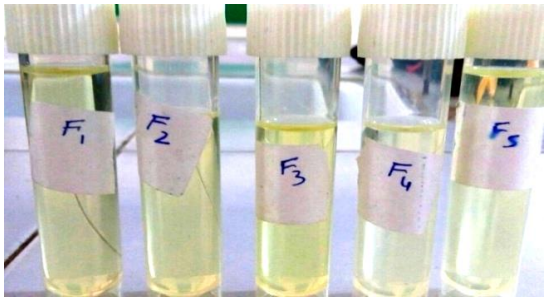

Figure 4: Different Nanoemulsion formulation.

Preparation of standard stock solution -100 mg of drug dissolve in 10 ml of methanol in 100 ml volumetric flask and volume was adjusted with methanol upto the mark to obtained 1000 µg/ml (solution A). The solution was filtered through whatman filter paper No. 41

Determination of λ_{max}

A10 ml solution was pipette out from solution A in 100 ml volumetric flask and diluted with methanol up to the mark to obtained 100 µg/ml. The solution was filtered through Whattman filter paper No. 41(solution B). From these aliquots of 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml and 1 ml were pipette out in to a 10 ml volumetric flask and diluted to methanol up to the mark and get the concentration 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10

µg/ml respectively. Absorbance of this solution was measured at 282 nm using UV spectroscopy against blank (methanol).

Table 1: Screening and selection of oil, surfactant and co-surfactant.

Excipients	Solubility (mg/ml)
Oils	
Olive oil	32.92
Castor oil	19.12
Oleic acid	49.22
Isopropyl myristate	43.16
Clove oil	39.36
Surfactants	
Tween 80	98.42
Span 20	106.31
Polyethylene gycol 4000	72.18
Co- Surfactants	
Propylene glycol	86.04
Glycerine	63.82

Preparation of phosphate buffer pH 7.4 (PBS)

Dissolve 2.3 gm of disodium hydrogen phosphate, 0.19 gm of potassium dihydrogen phosphate and 8 gm of sodium chloride in sufficient water to produce 1000 ml.

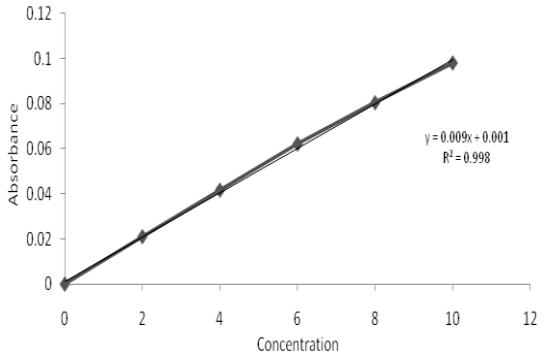

Figure 5: Calibration curve of terbinafine in 7.4 pH Phosphate buffer.

Calibration curve of terbinafine in Phosphate buffer pH 7.4 solution

A10 mg of drug dissolve in 20 ml of methanol and 8 ml of phosphate buffer in a 100 ml volumetric flask and volume was adjusted up to the mark to obtained 1000 µg/ml. The solution was filtered through whatman filter paper No. 41(solution A). From this solution an aliquot of 1 ml was withdrawn and diluted to 10 ml with PBS pH 7.4 to get concentration of 100 µg/ml (solution B), filtered out all solution by whatman filter no. 41. From these aliquots of 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml and 1 ml were pipette out in to a 10 ml volumetric flask and diluted to PBS pH 7.4 up to the mark and get the concentration 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml respectively. Absorbance of this solution was measured at 282.7 nm using UV spectroscopy against blank 2:8. (Methanol: PBS pH 7.4)

Construction of pseudo ternary phase diagram

The phase diagram was developed using water titration method to determine the appropriate components and their concentration ranges. Oleic acid was used as the oil phase, span 20 and propylene glycol was selected as surfactant and cosurfactant, respectively[8]. Distilled water was used as an aqueous phase. Surfactants and cosurfactant [S_{mix}] were mixed in different weight ratios (1:1, 1:2 and 2:1) to determine the optimum ratio which can result in maximum nanoemulsion area. For each phase diagram, oil and specific S_{mix} were mixed well in different ratios from 1:9 to 9:1 in different vials. The ratio of oil to surfactant varied as 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1. The mixtures were titrated with the aqueous phase, and visual observations were made for transparent and easily flow able oil-in-water (o/w) nanoemulsion. The physical state of the true nanoemulsion was marked on a pseudoternary phase diagrams with one axis representing the aqueous phase, and the other representing a mixture of surfactant and cosurfactant at fixed weight ratios (S_{mix} ratios).

Formulation of Terbinafine loaded nanoemulsion

The experimental design based on a three component system: Oil phase (oleic acid), S_{mix} (span20: propylene glycol) and aqueous phase (water). The total conc. of the three phases summed is 100%. Based on the results of pseudo ternary diagram appropriate range of the component was selected. The o/w NE was prepared by water titration method. The formulations were further sonicated (Sonica ultrasonic, 2000 MH) for 5 minutes and stored at room temperature until their use in subsequent studies.

Characterization of nanoemulsion

Physical characterization

The prepared nanoemulsion formulations were inspected visually for their color, appearance, consistency, phase separation and homogeneity.

Table 2: Particle size analysis of drug loaded nanoemulsion formulations.

Formulation code	Polydispersity Index	Particles size (nm)
F1	0.728	521
F2	0.709	95.96
F3	0.652	536
F4	0.400	144
F5	0.462	215.8

Droplet size and size distribution

The globules size distribution, polydispersity index and droplet size of the resultant nanoemulsion was determined by dynamic light scattering with zeta sizer, 1 ml of the optimized nanoemulsion formulation was diluted with water to 10 ml in a test tube, and gently mixed by glass rod and then analyzes the fluctuations in light scattering due to Brownian motion of the particles. Light scattering was monitored at 25°C at a 90° angle. Globule diameter and distribution was obtained.

Zeta-potential analysis

Zeta potential is a technique which is used to measure the surface charge properties and further the long term physical stability of nanoemulsion. The potential is measure of the electric potential at the slip plane between the bound layer of diluents molecules surrounding the particle and the bulk solution. A higher

level of zeta potential results in greater electro-static repulsion between the particles, minimizing aggregation/flocculation[10].

Measurement of pH

1 ml of nanoemulsion was dissolved in 10 ml of distilled water. At first pH meter reading was calibrated using known pH solution (pH4 and pH7) and the electrode was then dipped in to NE formulation and constant reading was noted[11].

Table 3: Viscosity of Nanoemulsion formulation.

Spindle speed (rpm)	Formulation code				
	F1	F2	F3	F4	F5
0.3	960	982	861	946	883
0.6	829	830	720	871	739
1.5	740	724	648	730	647
3	629	604	525	627	521
6	552	526	424	552	458
12	385	437	335	382	317
30	240	352	227	218	241

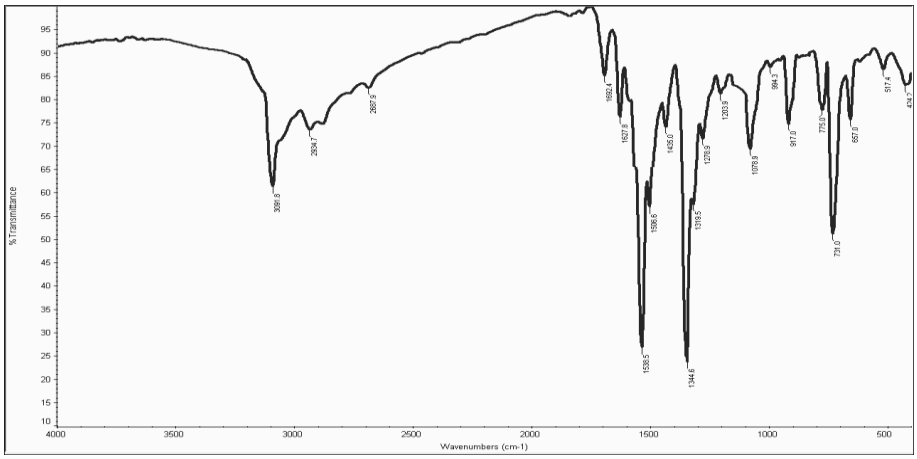

Figure 6: FTIR spectra of nanoemulsion (Terbinafine+ Oleic acid+ Span20+ Propylene glycol).

Measurement of viscosity

The viscosity of true nanoemulsion was determined without any dilution using Brookfield viscometer. The sample (30 ml) was taken in a beaker and allowed to equilibrate for 5min before measuring the reading using a spindle at 2, 2.5, and 5, 6, 10, 12, 20, 30 rpm. At each speed, the corresponding reading on the viscometer was noted[12].

Table 4: Viscosity of nanoemulsion gel formulation.

Spindle speed (rpm)	Formulation code				
	F1	F2	F3	F4	F5
0.3	9600	12000	6000	8400	6500
0.6	4000	8000	4000	6200	2200
1.5	2000	7600	2600	2300	1650
3	1700	3700	1820	1200	940
6	1400	2300	1300	730	820
12	1158	1600	780	620	760
30	720	900	480	320	550

Centrifugation

This technique of centrifugation helps to determine the phase separation of nanoemulsion. 10 ml NE was placed in centrifugation tube and put in apparatus at 3000 rpm for 30 min and examined for any phase separation.

Dye test

It is used to check the nature of the nanoemulsion (o/w or w/o). Water soluble dye is added in o/w NE. The NE takes up the color uniformity. Conversely, if the emulsion is w/o type and the dye being soluble in water, the emulsion takes up the colour only in dispersed phase and emulsion is not uniformly colored[13].

Table 5: Spreadability and percentage drug content of nanoemulsion gel.

Formulation Code	Spreadability	% Drug content
F1*	5.14	88.9
F2*	5.46	90.3
F3*	6.15	81.9
F4*	6.47	92.7
F5*	6.31	86.3.7

Formulation of nanoemulsion gel

1% carbopol 934 was selected as a gelling agent. Carbopol 934 solution (1% carbopol 934 added in warm water with continuous stirring) added drop wise into the nanoemulsion with continuous stirring until the nanoemulsion convert into nanoemulgel[14].

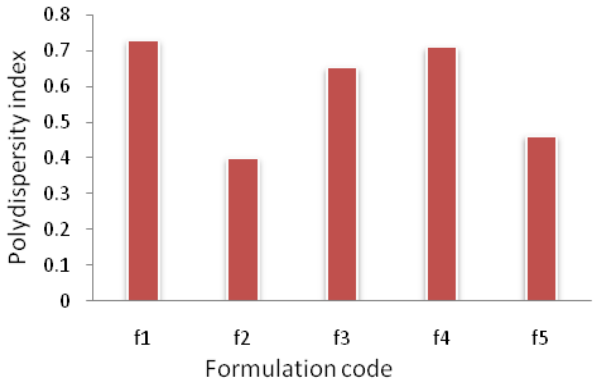

Figure 7: Graphical representation of polydispersity index.

Characterization of nanoemulgel

pH determination

One gram of nanoemulgel was dissolved in 10 ml of distilled water and the pH meter was prior standardized with standard buffers of pH 4 and pH 7[14].

Viscosity

The viscosity of formulations is determined using Brookfield DV-III at temperature 25°C. 50grams of the sample is tested using a 50 ml capacity vessel using spindle 5 at different speed[12].

Spreadability

An excess of emulgel (about 1g) under study was placed on this ground slide. The emulgel preparation was then sandwiched between this slide and second glass slide having same dimension as that of the fixed ground slide. The second glass slide is provided with the hook[15]. Weight of 100 g was placed on the top of the two slides for 5 min to expel air and to provide a uniform film of the emulgel between the two slides. Measured quantity of weight (35 g) was placed in the pan attached to the pulley with the help of hook. Time in seconds taken by two slides to slip off from emulgel and placed in between the slides under the direction of certain load. Lesser the time taken for separation of two slides, better the spreadability. It is calculated by using the formula.

$$S = \frac{m \times l}{t}$$

Where S is spreadability, m is weight placed on upper slide, l is length of upper slide, and t is the time taken.

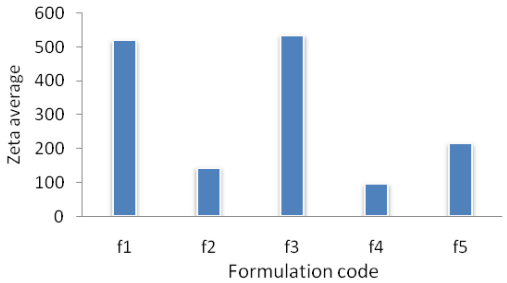

Figure 8: Graphical representation of zeta average.

Drug content determination

Quantity of Terbinafine in nanoemulsion gel was determined by UV-Spectrophotometer. 1.0 g of formulation was accurately weighed, dissolved in 100 ml of methanol: phosphate buffer (2:8). It was filtered and diluted if required. Absorbance was determined using UV spectrophotometer at 282.7 nm[16].

***In-vitro* release study**

The *In-vitro* drug release studies were carried out using a modified Franz diffusion cell (With effective diffusion area 2.54 cm^2 and 20 ml cell volume). The formulation was applied on dialysis membrane (which was previously soaked in Phosphate buffer pH 7.4 for 24 hours) which was sandwiched between donor and receptor compartment of the Franz diffusion cell. Phosphate buffer pH 7.4 was used as dissolution media. The temperature of the cell was maintained at 37±0.2°C by kept it in water bath. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead at 50 rpm. The samples (1 ml aliquots) were withdrawn at suitable time interval and analyzed for drug content by UV visible spectrophotometer at 282.7 nm after appropriate dilutions[17].

***In-vitro* drug release kinetics**

To study the release kinetics of in-*vitro* drug release, data was applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer-Pappas[18,19].

In short, the result obtained from *in-vitro* release studies were plotted in four kinetic models of data treatment as follows:

- Cumulative % drug release Vs. Time (zero order rate kinetics)
- Log cumulative % drug release Vs. Time (First order rate kinetics)
- Cumulative % drug release Vs. Time √T (Higuchi's classical diffusion equation)
- Log cumulative % drug release Vs. log Time (Korsmeyer Peppas equation).

Statistical analysis

Experimental results were expressed as mean±SD. Student's *t*-test and one-way analysis of variance (ANOVA) were applied to check significant differences in drug release from different formulations. Differences were considered to be statistically significant at $p<0.05$.

RESULTS AND DISCUSSION

The pre-formulation studies were performed as per given procedures. The partition coefficient (log P) was determined by shake flask method. The log *P* value of drug sample was obtained 5.51.Total 10 mg Terbinafine was dissolve in 10 ml of ethanol than 1 ml of this solution was taken and diluted up to 10 ml with ethanol. This dilution were scanned for determined absorption maxima in range 200-300 nm. The observed absorbance maxima were found to be 282.7 nm. The calibration curve of Terbinafine in 7.4 pH PBS was determined in conc. range of 2-10 µg/ml. The compatibility of nanoemulsion containing all excipients oleic acid as oily phase, span20 as a surfactant and propylene glycol as a co-surfactants and drug (Terbinafine), by FTIR. It was found that there was no chemical reaction between drug and excipients because in the characteristics peaks of terbinafine, there no any changes was observed when compared to the IR spectra of pure drug. In the all formulation the particle size range were observed from 95.96 to 536 (nm) and the polydispersity index was found to be 0.400 to 0.709. The particle size study explain that the effect of different ratio of surfactant, cosurfactant, oil and water. F4 has 144 nm zeta average due to 1:2 proportion of surfactant and cosurfactant and less amount of oil phase. Higher size average was found to be 536 nm for formulation F1. From the all 4 formulations, best formulations graphs and figure are given below. First graph is F2, its size was found to be 95.96 nm and polydispersity index was found to be 0.709. Second graph is F4, its size was found to be 144 nm and polydispersity index was found to be 0.400. Third graph is F5, its size was found to be 2.15.8 nm and

polydispersity index was found to be 0.462. Zeta Potential of all formulation was found to be -4.32 to -32.6. The higher zeta potential of any formulation shows more stability because due to the high zeta potential of particles are not allow getting aggregate because of electrical repulsive force between particles.

The pH value for NE formulation was recorded 5.73 to 6.82. The pH of the NE was found to be within the range of pH of skin and would not cause any irritation to the skin. A Brookfield Viscometer was used to measure the viscosity of nanoemulsion and nanoemulgel by different spindle speeds. Viscosity reveals the rheological properties of all formulation.

Spreadability of NEG was determined by spreadability apparatus. Spreadability is measured on the basis of 'slip' and 'Drag' characteristics of nanoemulsion gel. Spreadability is an important property of topical formulation from patient compliance point of view.

Drug content is the drug concentration in gellified nanoemulsion, which was measured by UV spectrophotometer. The range of percentage drug content of nanoemulsion gel was 75.3% to 92.7%. The range of percentage drug content of formulations was found to be satisfactory. The *in-vitro* % cumulative drug release studies of NEG were found to be 66.90% to 82.69%.

All the formulation shows different release rate because of different ratio of surfactant and co-surfactant. F4* NE shows best drug release 82.69% in 6hrs and F2* shows lowest drug release 66.90% in 6hrs. For the determination of drug release data of all NEG formulation were fitted into zero order kinetics, first order kinetics, Koresymer Peppas release kinetics, Higuchi release kinetics, Bakar losandale release kinetics to know the drug release pattern from the NEG formulation.

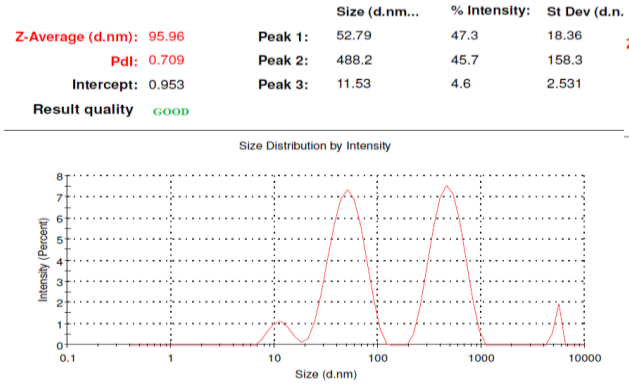

Figure 9: Particle size Analysis of drug loaded Nanoemulsion (Formulation F2).

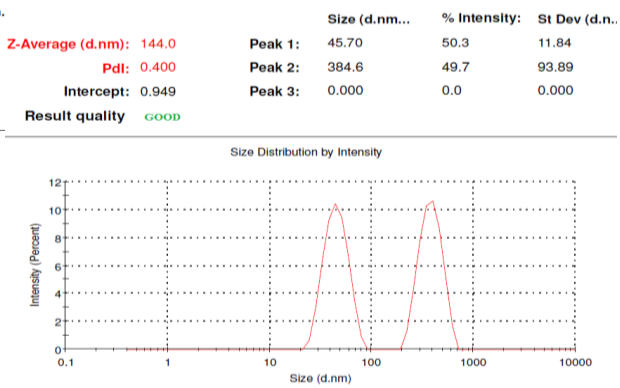

Figure 10: Particle size Analysis of drug loaded Nanoemulsion (Formulation F4).

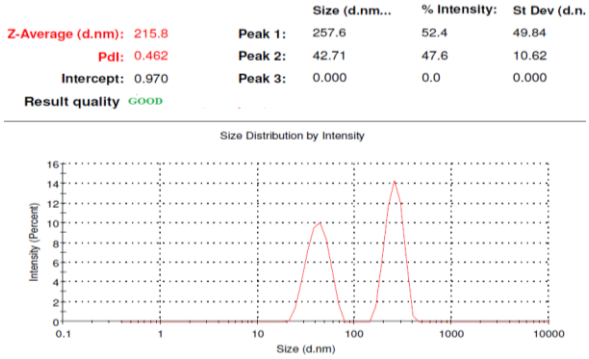

Figure 11: Particle size Analysis of drug loaded Nanoemulsion (Formulation F5).

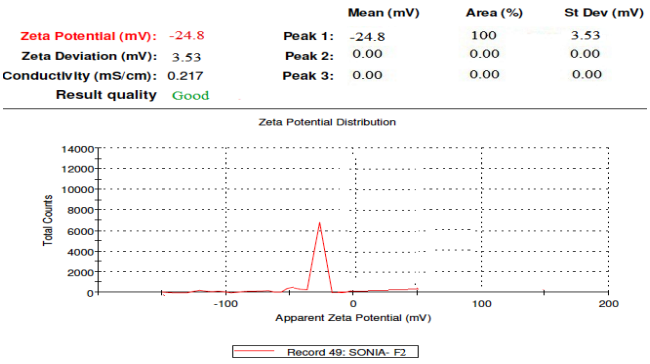

Figure 12: Zeta potential of drug loaded nanoemulsion F2.

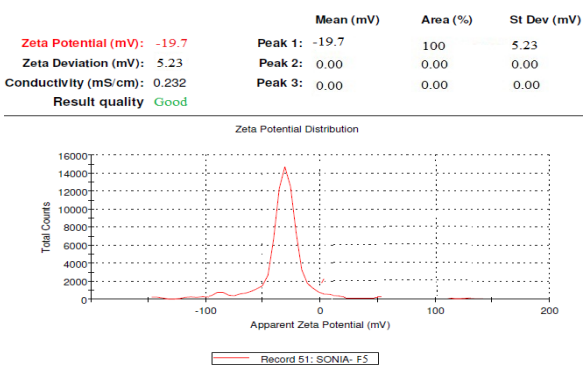

Figure 13: Zeta potential of drug loaded nanoemulsion.

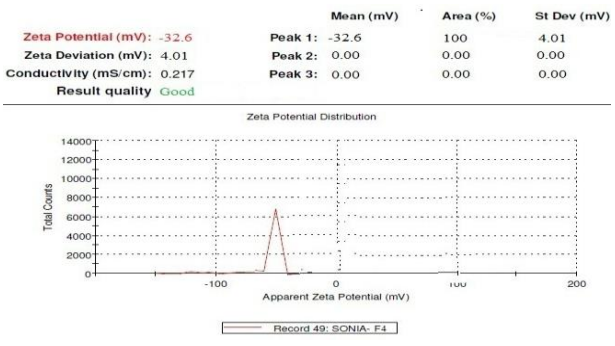

Figure 14: Zeta potential of drug loaded nanoemulsion.

Table 6: Drug release kinetics parameters of nanoemulsion gel formulations.

		F1	F2	F3	F4	F5
Zero order	R^2	0.928	0.933	0.948	0.982	0.982
	n	0.002	0.002	0.002	0.002	0.001
First order	R^2	0.982	0.978	0.994	0.983	0.986
	n	-0.001	-0.00	-0.001	-0.001	-0.000
Higuchi Model	R^2	0.970	0.965	0.972	0.969	0.966
	n	0.043	0.040	0.045	0.046	0.036
Korsmeyer-Peppas	R^2	0.969	0.975	0.985	0.996	0.997
	n	0.885	0.932	0.838	0.781	0.805
Bakar Losandale	R^2	0.985	0.983	0.977	0.931	0.923
	n	0.000	0.000	0.000	0.000	0.000

The results of model dependent methods for curve estimation were used to develop regression models that have the best R^2 values. It is evident from the regression value of NEG followed the drug release of formulation F1* and F2* followed the Baker losandale release pattern because R^2 was 0.985 and 0.983 and n value was found to be 0.000 and 0.000 this is may be due to their surf: cosurf ratio. F3* followed the first order release pattern because R^2 was 0.994 and n value was found to be -0.001. F4* and F5* followed the Koresymer release pattern with non-Fickian anomalous diffusion ($0.45<n<0.89$) because R^2 was 0.996 and 0.997 and n value was found to be 0.781 and 0.805. F4* and F5* shows best R^2 value.

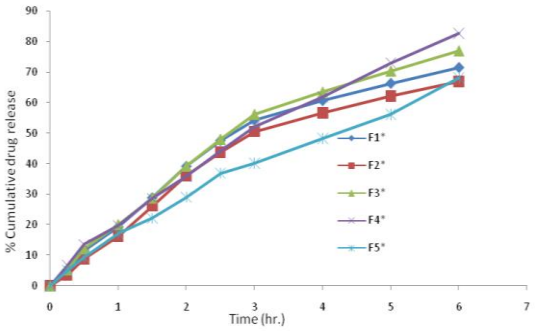

Figure 15: Graphical representation of % cumulative drug release of NEG.

CONCLUSIONS

The principle object of the present experimental work was to make a most effective topical preparation for avoid the first pass metabolism of terbinafine in the treatment of antifungal infections with maximum drug release and reduce GIT side effects. There was a spontaneous formation of clear nanoemulsion, presumably due to orientation of surfactant and cosurfactant at the interface, which is a direct consequence of high thermodynamic stability at the attained interface of the system. In this study, nanoemulsion and NEG were prepared and evaluated. The results showed that nanoemulsion components had significant effect on the response. The nanoemulsion formulation containing % surf: co surf 48.91, % oil 5.43 and % water 45.65 was best for forming NEG. For all studies the nanoemulsion gel F4* has best release and most effective formulation. Study concludes that nano emulgel is a promising area for continued research with the aim of achieving controlled release with enhanced bioavailability and for drug targeting to affected sites.

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AUTHOR'S CONTRIBUTION

Paliwal S: writing, review, and editing. **Kaur G:** methodology, data curation. **Arya KKR:** writing, review, and editing, data curation. All authors read and approved the final manuscript for publication.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

None to declare.

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