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Formulation and Evaluation of Microemulsion Based Hydrogel of Tolnaftate for Topical Delivery

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ABSTRACT

The purpose of this study was to formulate and evaluate microemulsion based hydrogel for topical delivery of a drug tolnaftate to treat fungal infections to increase the solubility and controlled drug delivery. Microemulsions were prepared by mixing the fixed ratio of surfactant and co-surfactant to oil followed by the drug, the ratio of surfactant and co-surfactant was selected by the pseudo-ternary phase diagram. The different ME formulations are evaluated for drug content, % transmittance, dilution potential, thermodynamic stability testing, viscosity, zeta potential, particle size, and *in-vitro* drug release study to select the optimized formulation. To the optimized formulation of different concentrations of Hydroxypropyl, cellulose polymer was added to form the hydrogel. The formulations were evaluated for physical evaluation, viscosity, pH, drug content, spreadability, *in-vitro* drug release, and kinetic studies. Among the developed formulation FF2 was found to be a better formulation. The drug content of FF2 formulation was found to be 95.38%. The drug release from the FF2 (hydrogel) formulation was found in 85.79% at the end of 6 hrs. The release kinetics follows the zero-order peppas model. Based on the results it can be concluded that microemulsion based hydrogel of tolnaftate is useful for the treatment of topical fungal diseases effectively with improved solubility and controlled delivery of the drug.

INTRODUCTION

Fungal infections are called Mycoses and can be divided into superficial infections (affecting the skin, nails, hairs, or mucous membranes) and systemic infections (affecting deeper tissues and organs). Studies have shown that there is an increase in systemic fungal infections, not only by known pathogenic fungi but also by fungi formerly thought to be innocuous [1].

The topical drug delivery system can be defined as the direct application of a formulation containing medication to the skin to get the localized effect of the drug. Most and encouraging reason for using a topical delivery is the avoidance of gastro-intestinal incompatibility and metabolic degradation associated with oral administration. Moreover, topical delivery provides an increased bio-availability by avoiding first-pass metabolism by the liver and consistent delivery for an extended period [2].

The microemulsion was prepared by dispersing oil in an aqueous surfactant solution and adding alcohol as co-surfactant, leading to a transparent stable formulation [3].

The microemulsion is defined as clear, transparent, thermodynamically stable dispersions of oil and water stabilized by an interfacial film of surfactant frequently in combination with a co-surfactant [4]. Microemulsions are bicontinuous systems that are essentially composed of bulk phases of water and oil separated by a surfactant/co-surfactant rich interfacial region [5].

Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of absorbing large amounts of water or biological fluids. Due to their high water content, porosity, and soft consistency, they closely simulate natural living tissue, more than any other class of synthetic biomaterials [6]. Hydrogels can be formulated in a variety of physical forms, including slabs, microparticles, nanoparticles, coatings, and films. As a result, hydrogels are commonly used in clinical practice and medicine with a wide range of applications, including tissue engineering and regenerative medicine, diagnostics, cellular immobilization, separation of biomolecules or cells, and barrier materials to regulate biological adhesions [7].

Tolnaftate is a synthetic over-the-counter anti-fungal agent. It is used to treat skin infections such as athlete's foot, jock itch, and ringworm infections [8]. It is also used, along with other antifungals, to treat infections of the nails, scalp, palms, and soles of the feet. Though its exact mechanism unknown, it is believed to prevent ergosterol biosynthesis by inhibiting Squalene epoxidase. It has also been reported to distort the hyphae and to stunt mycelial

growth in susceptible organisms [9]. The present study is focusing on the formulation and evaluation of novel approaches in the management and therapy of fungal diseases, with ease of absorption, avoiding first-pass metabolism, and controlled drug delivery.

MATERIALS AND METHODS:

Tolnaftate has obtained from yarrow chemicals Mumbai, Castor oil, Soybean oil, Corn oil, Peanut oil,Sesame oil obtained from Deveherbes New Delhi, Oleic acid, Ethanol was obtained from the SD fine chem. Mumbai. All other chemicals used were of laboratory reagent grade.

1. Formulation of Microemulsion

Determination of solubility of tolnaftate in various oils, surfactants, and co-surfactants

Screening of various oils, surfactants and co-surfactants were done for tolnaftate solubility. Solubility studies were conducted by placing an excessive amount of tolnaftate (approximately 200 mg) in a tube containing 1ml of each vehicle. Then the mixture was kept on a rotary shaker for 48 hours to facilitate solubilization. The sample was centrifuged at 3000 RPM for 15 min to remove un-dissolved tolnaftate. The supernatant was diluted to 10 times and filtered through Whatman filter paper for quantification of tolnaftate by UV-spectroscopy [10].

1.1 Screening of oils/vehicles:

The oil in which the solubility of the drug was more was selected for further study. From the selected oil, the oils which had optimum physical properties were finalized for formulation.

1.2 Screening of surfactant:

Surfactants were selected based on the following criteria.

(a) Based on the ability to solubilize the drug:

The surfactant which could solubilize the highest amount of tolnaftate was considered.

(b) Based on ease of emulsification

Different surfactants were screened for the emulsification ability of the selected oil phase. Surfactant selection was performed based on % transparency and ease of emulsification. Briefly, 0.3 ml of the surfactant was added to 0.3 ml of the selected oil phase. The mixture was gently heated at 50 ˚C for the homogenization of the component. 0.1 ml of the mixture was diluted with distilled water to 50 ml in a volumetric flask. Ease of emulsification was judged by the number of flask inversions required to yield a homogenous emulsion. The emulsion was allowed to stand for 2 hr and their % transparency or transmittance was determined at 650nm by double beam UV spectrometer using distilled water as blank. The emulsions were furthermore observed visually for any turbidity and phase separation.

1.3 Screening of Co-solvents:

Co-solvents were selected based on the following criteria.

(a) Based on the solubility of the drug

The co-solvents which could solubilize the highest amount of tolnaftate were considered.

1.4 Construction of pseudo ternary phase diagram to select the best combination of oil, surfactant, and co-surfactants.

To find out the existence range of microemulsion, pseudo ternary phase diagrams were constructed using the water titration method at ambient temperature (25 °C). Based upon the available solubility profile of the drug, oleic acid was selected as an oil phase; tween 80 and polyethylene glycol 200 was used as surfactant and co-surfactant respectively. The S_{mix} (surfactant+ Co-surfactant) ratios were selected to be 1:1, 2:1 and 3:1 v/v and used. For each phase diagram at specific S_{mix} concentration, the oleic acid was added from the range of 1:9 to 9:1 and the mixture was diluted with distilled water. Water was added by drop by drop while mixing on a magnetic stirrer at room temperature, and the samples were marked as being optically clear or turbid. The microemulsion regions were identified 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.1). From the endpoint compositions of titrated samples the mass percent composition of the components like oil, $S_{mix,}$ and water was calculated and then plotted on triangular coordinate to construct the pseudo ternary phase diagram. The experiment was performed in triplicate to check the reproducibility [11].

1.5 Formulation selection:

Based on the pseudo ternary phase diagram studies, the formulations were selected which showed the highest areas of the microemulsion. Considering these criteria, nine formulations were selected as follows.

Table No. 1: Formulation of Tolnaftate micro-emulsion

S_{mix}	Formulation code	Drug	Percent w/w of components in the formulation		
			Oil (%)	S_{mix} (S+CoS %)	Water (%)
1:1	F1	1%	2.75	45.66	51.65
	F2	1%	18.4	55.66	25.94
	F3	1%	13.42	64.88	21.70
	F4	1%	13.58	65.85	20.57
2:1	F5	1%	8.75	66.7	24.55
	F6	1%	7.57	67.73	24.70
	F7	1%	8.75	68.37	22.80
	F8	1%	4.54	76.11	19.35
	F9	1%	8.24	81.51	10.57

1.6 Preparation of microemulsion

After identification of the microemulsion regions in the phase diagram, the microemulsion formulations were selected for Smix at desired component ratios.O/W ME of tolnaftate was prepared by water titration method. Briefly, weighed amount of surfactant and co-surfactant are in fixed ratio to oil then add the drug tolnaftate. Sonicate the above mixture for 5 min to dissolve the drug and allow cooling to room temperature. Add required quantity of water drop wise with magnetic stirrer and allow forming a clear and transparent liquid to form homogenous and stable microemulsion.

A series of ME were prepared using tween 80 and PEG as the S/CoS combination and oleic acid as the oil. In all formulations, the concentration of tolnaftate was kept constant (1g) and a varying ratio of oil, surfactant, co-surfactant was added. Various formulation ratios are given in Table.1.

2.0 Characterization and evaluation of microemulsion

2.1 Drug content:

Microemulsion containing 10 mg drug was dissolved in 100 ml of pH 7.4 buffer taken in a volumetric flask. The solution was filtered, 1ml of the above solution was taken in a 50 ml volumetric flask and diluted up to mark with pH 7.4 buffer and analyzed spectrometrically at 262 nm. The concentration of tolnaftate in mg/ml was obtained by using a standard calibration curve of the drug [12].

2.2 % Transmittance:

Transparency of microemulsion formulation was assessed by measuring the percentage transmittance of the sample at 650nm by using water as blank [13].

2.3 Dilution potential/Robustness on dilution:

The microemulsions formulations are diluted as 1:10 and 1:100, ratios with distilled water. The emulsion was observed for any precipitation, to confirm the stability of the emulsion [14].

2.4 Stability testing

a) Centrifugation test

The Centrifugation test to find the stability of formulation by analyzing the phase separation by using the Remi centrifuge instrument at 5000 rpm for 15 min. The formulation does not undergo phase separation and was taken to the next stability testing methods [15].

b) Stress test

Stability of formulations was detected by placing in 10ml transparent borosil volumetric flask at three different temperatures i.e. 4, 25, and 45 ° ± 1° in a temperature-controlled oven or an incubator for 48-72 hours. Samples were removed periodically for assessment to detect any physical changes like loss of coalescence, clarity, and turbidity, etc [12].

c) Freeze-thaw method

The freeze-thaw methods were employed where temperature ranging from -4 to 40 ° for 24 hours. Samples were periodically checked visually to find any physical changes like clarity loss, the presence of coalescence and turbidity, etc [15].

2.5 Viscosity:

The viscosity of the formulations was determined using Brookfield Viscometer without dilution. The viscosity of the samples was measured at 25 ° with spindle no 63. The sample temperature was controlled at 25 ± 1° before each measurement [10].

2.6 Zeta potential

Zeta potential of samples was measured by zeta sizer. Samples were placed in clear disposable zeta cells and results were studied.

2.7 Particle size/ size distribution of microemulsion

Particle size analysis was carried out using a zeta sizer. The sizing measurements were carried out at a fixed angle of 173 ° [16].

2.8 *In-vitro* drug release

In-vitro drug release studies were performed using Franz diffusion cell employing a cellophane paper. The paper was clapped between the donor and receptor compartments of the Franz diffusion cell. The receptor compartment was filled with pH 7.4 buffer solution and was magnetically stirred throughout the experiment at 100 rpm. The donor compartment contained an appropriate amount of formulation. 1ml sample was withdrawn from the receptor compartment at specified time intervals for 6 h and replaced with the fresh buffer solution. The samples were analyzed by UV-Visible spectroscopy at 262 nm [17].

3.0 Preparation of hydrogel

The HPC as a gel matrix was used to construct the microemulsion based hydrogel for improving the viscosity of microemulsion for topical administration. The weighed quantity of the hydroxypropyl cellulose was dissolved in 10ml of distilled water and stirred thoroughly to get homogenous slurry. The hydrogel was slowly mixed with microemulsion under stirring.

As the microemulsion was added to the hydrogel, the viscosity of the micro emulsion-based hydrogel was decreased. Hence, to obtain sufficient viscosity of micro emulsion-based hydrogel, the hydrogels were prepared at various concentrations (1, 1.5, and 2%w/w) [10].

4.0 Characterization and evaluation of hydrogel

4.1 Physical evaluation

Microemulsion based gel inspected for their color, consistency, homogeneity, texture, etc [18].

4.2 Viscosity

The viscosity of microemulsion based hydrogel was determined using a viscometer (Brookfield. the USA) at 50 rpm with spindle # LV4 at room temperature [19].

4.3 pH

The pH of hydrogel formulations was determined by using digital pH meter. The measurement of pH of each formulation was done in triplicate and average values were calculated, using a calibrated digital pH meter at 25 ° [20].

4.4 Drug content

Weigh accurately 1 gm of hydrogel and dissolved in 100 ml of phosphate buffer pH 7.4. The volumetric flask was kept in a shaker for 4 hr to mix it properly. The solution was filtered, 1 ml of the filtrate was taken into 10ml volumetric flask and the final volume was made with 7.4 phosphate buffer. The absorbance was measured spectroscopically at 262nm after appropriate dilution against corresponding phosphate buffer pH 7.4 as blank [20].

4.5 Spreadability

To determine the spreadability of MBHs were transferred to the center of a glass plate (10 cm x 10 cm) and this glass plate was compressed under another glass plate of the same size. Thus, the gel was spread out between the plates. After one minute, the weight was removed and the diameter of the spread area (cm) was measured. The measurement was performed in triplicate [21].

4.6 *In-vitro* drug release

The *in-vitro* drug release studies were performed by using Franz diffusion cell with cellophane paper. The water-jacketed recipient compartment had a total capacity of 30ml and it had one arm for sampling and another side for water inlet and outlet. The donor compartment had an internal diameter of 2.8 cm^2. The donor compartment was placed in such a way that it just touches the diffusion medium in the receptor compartment. The receptor compartment contained phosphate buffer solution pH 7.4. That was maintained at 37 °±1 °C. The membrane was equilibrated before the application of the MBH onto the donor side. 1ml of samples was periodically withdrawn from the receptor compartment, replacing with the same amount of fresh PBS solution, and assayed by using a spectrophotometer at 262 nm [19].

5. Release kinetics [22, 23]

The release kinetics was evaluated considering four different models including zero order, first order, Higuchi's equation, and Korsmeyer Peppa's model.

- **Higuchi kinetics**

The graph was plotted as % Cumulative drug release Vs square root of time.

$$F = kt_{1/2}$$

Where, k = the release rate constant

F = the amount of drug release

t = the release time

- **Zero-order release**

The graph was plotted as % Cumulative drug release Vs time. To study the zero-order release kinetics the release rate data are fitted to the following equation.

$$F= K.t$$

Where, F = the fraction of drug release

K = the release rate constant

t = the release time

- **First-order release kinetics**

The graph was plotted as a Log % cumulative drug released Vs time. First-order reaction is defined as a reaction in which the rate of reaction depends on the concentration of one reactant. The expression for first-order given below:

$$Kt = 2.303 \log C_0$$

Where C_0 = concentration at time t = 0

- **Korsmeyer and Peppas release model :**

The graph was plotted as log % drug unreleased Vs log time. The release rate was fitted to the following equation.

$$Mt / M\infty = k\, t^n \text{ or}$$

$$\ln (Mt/M\infty) = n \ln (t) + \ln (k)$$

Where Mt / M∞ = the amount of drug released at time t

Mt = the amount of drug released at time t

M∞ = the amount of drug released over a long time t

k = the release rate constant

t = the release rate time

n = the diffusion exponent for the drug release that is dependent on the matrix dosage form

RESULTS AND DISCUSSION:

1. Formulation of microemulsions:

(i) Screening of oils

Table No 2: Solubility of the drug in various oils

Sr. No.	Oil	Solubility (mg/ml)
1	Castor oil	28.5
2	Soyabean oil	16.8
3	Sesame oil	22.7
4	Oleic acid	38.74
5	Corn oil	20.8
6	Peanut oil	15.4

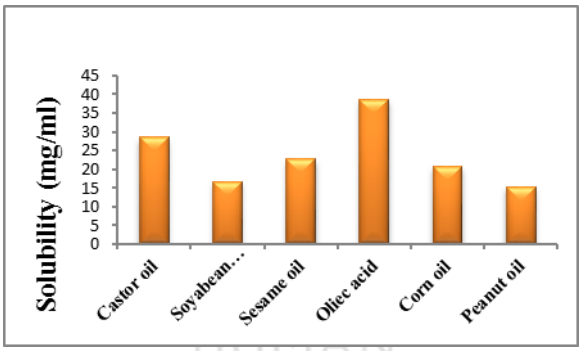

Figure No. 1: Solubility of the drug in various oils

Selection of oil

Oleic acid showed the highest solubility of tolnaftate (38.74 mg/ml). Hence oleic acid was used as an oil phase.

(ii) Screening of surfactant

Table No. 3: Solubility of the drug in various surfactant

Sr. No.	Surfactant	Solubility (mg/ml)
1	Tween 80	30.5
2	Span 8	24.3
3	Tween 20	18.6
4	Span 20	22.5

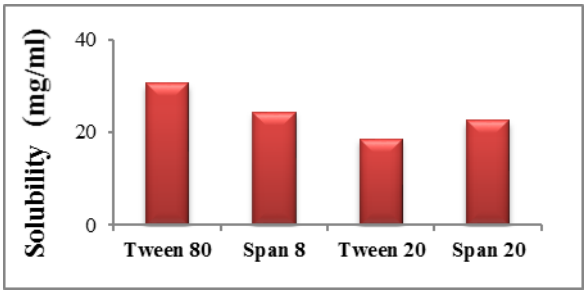

Figure No. 2: Solubility of drug in various surfactants

Selection of surfactant

Tween 80 showed the highest solubility of tolnaftate (30.5 mg/ml). Hence Tween 80 was used as a surfactant.

(iii) Screening of co-surfactants

Table No. 4: Solubility of the drug in various co-surfactants

Sr. No.	Co-surfactant	Solubility (mg/ml)
1	PEG	80
2	Ethanol	75.3
3	Glycerin	62.2
4	Isopropyl alcohol	71

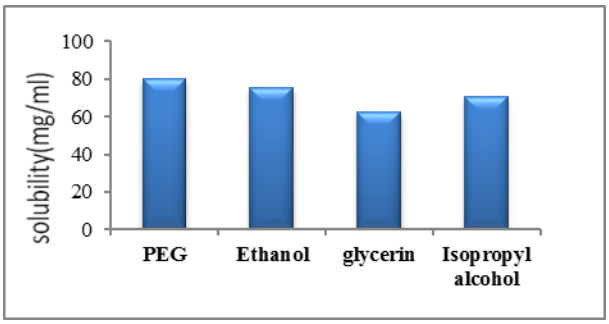

Figure No. 3: Solubility of the drug in various co-surfactants

Selection of co-surfactant

PEG showed the highest solubility of tolnaftate (80 mg/ml). Hence PEG was used as a co-surfactant.

❖ **Construction of Pseudo ternary phase diagram to select the best combination of oil/surfactant and co-solvent.**

Preparation of S_{mix} (Surfactant+ Co-surfactant)

Stock solution of 60 ml was prepared in different ratios of surfactant and co-surfactant, as follows,

1:1 = 30 ml surfactant + 30 ml co-surfactant ($S_{mix}A$)

2:1 = 40ml surfactant + 20 ml co-surfactant ($S_{mix}B$)

3:1= 45 ml surfactant + 40 ml co-surfactant (S_{mix} C)

1;2= 20 ml surfactant+ 40 ml co-surfactant (S_{mix} D)

Here Tween 80 was used as surfactant and PEG was used as co-surfactant.

Pseudo ternary phase diagram

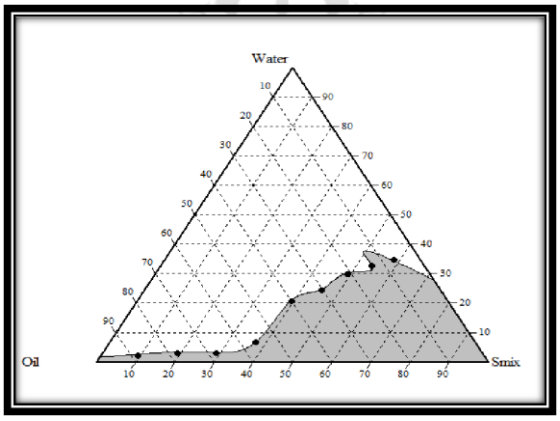

Figure No. 4: Ternary plot for the formulation of system A

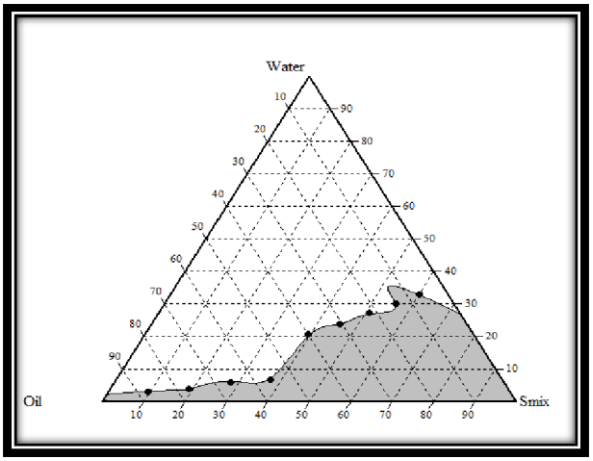

Figure No. 5: Ternary plot for formulation of system B

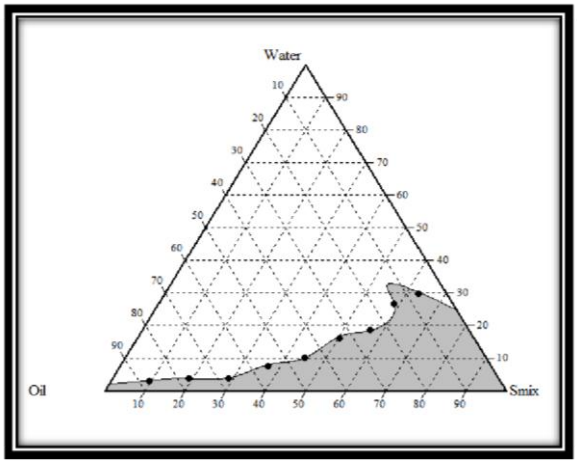

Figure No. 6: Ternary plot for formulation of system C

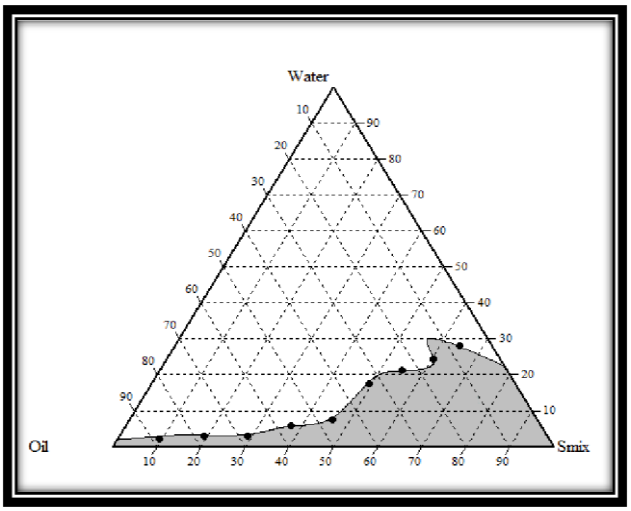

Figure No. 7: Ternary plot for formulation of system D

Formulation of system A and system B showed a wide area of microemulsion when compared to system C and D. Hence the system A and B were selected for further studies. There was no notable change found in the area of the microemulsion of system A and B even after the addition of tolnaftate drug.

Evaluation of microemulsions

Table No. 5: Evaluation of microemulsions

Formulation code	% Drug Content	% Transmittance	Viscosity (mPas)	Stress test, Freeze-thaw cycles, Dilution potential	Centrifugation test
F1	96.47	93.21±0.17	176.3	Stable, no precipitation	Stable, no precipitation and phase separation
F2	95.48	92.89±0.59	230.89	Stable, no precipitation	Stable, no precipitation and phase separation
F3	95.40	92.03±0.68	89	Stable, no precipitation	Stable, no precipitation and phase separation
F4	96.09	93.11±0.12	270.91	Stable, no precipitation	Stable, no precipitation and phase separation
F5	96.82	94.99±0.91	221.4	Stable, no precipitation	Stable, no precipitation and phase separation
F6	94.89	91.48±0.68	311.5	Stable, no precipitation	Stable, no precipitation and phase separation
F7	94.03	89.01±0.21	356.7	Stable, no precipitation	Stable, no precipitation and phase separation
F8	92.71	90.18±0.48	199.08	Stable, no precipitation	Stable, no precipitation and phase separation
F9	89.98	88.19±0.84	126.0	Stable, no precipitation	Stable, no precipitation and phase separation

Zeta potential and particle size

From all the result obtained F5 was found to be the ideal batch, for which the zeta potential was found to -25.3 mV. This indicates the stability of the best formulation.

Particle size analysis for best formulation F5 was carried out and the average particle size of F5 formulation was found to be 347.1nm.

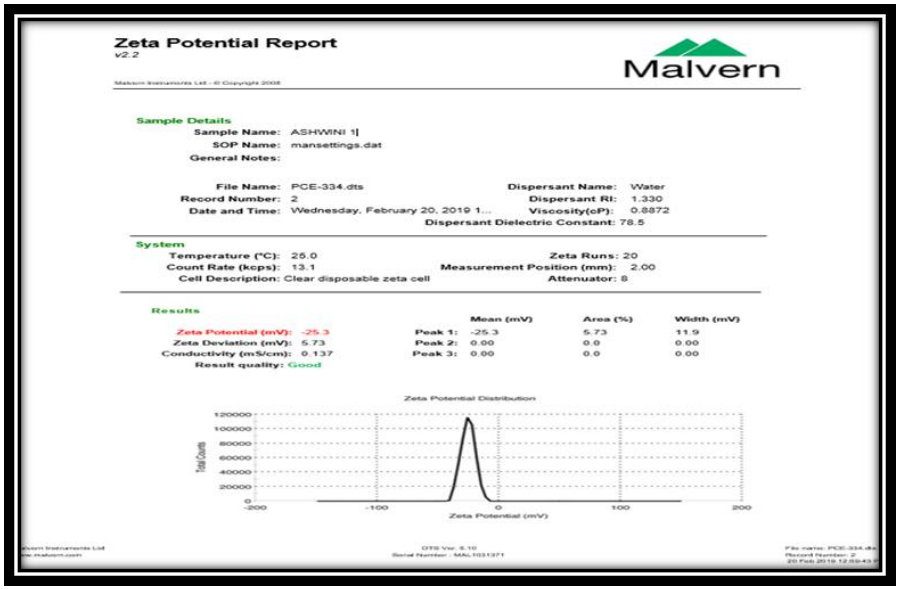

Figure No. 8: Zeta potential of formulation F5

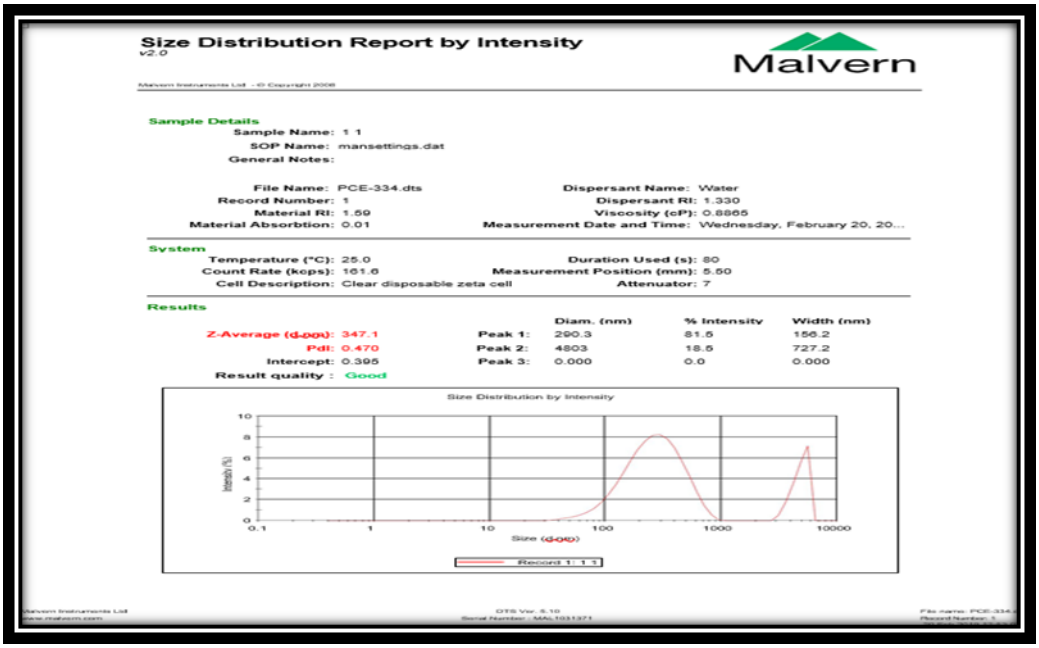

Figure No. 9: Average particle size of formulation F5

***In-vitro* drug release study of microemulsions**

Table No. 6: *In-vitro* drug release study of microemulsions

Time (hr)	Percentage Cumulative Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	11.65	10.91	7.14	7.13	13.62	5.13	8.17	7.13	10.45
2	17.03	21.09	13.73	15.93	27.67	13.18	18.58	19.08	17.14
3	25.04	33.44	24.13	25.13	37.84	27.03	29.09	30.14	28.50
4	39.58	41.01	36.81	39.07	46.75	44.03	43.04	35.58	35.88
5	54.05	57.47	47.79	54.13	58.54	56.07	52.85	51.50	48.58
6	65.09	63.89	59.64	60.85	68.60	64.81	67.58	61.54	59.45

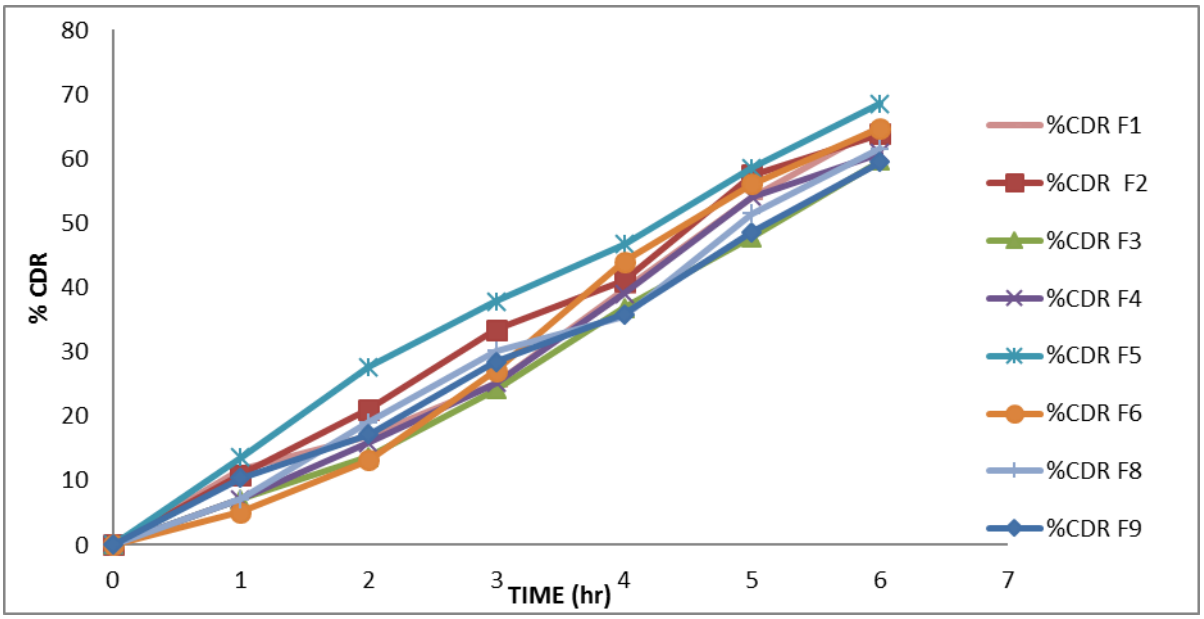

Figure No. 10: *In-vitro* drug release study of microemulsion formulations F1-F9

Among the 9 batches of formulations, it was found that formulation F5 showed a good release rate when compared to other formulations. The formulation F5 showed the percentage drug release of 68.60% in 6 hrs. Hence the formulation F5 was considered for further studies.

Formulation of microemulsion based hydrogels

Hydrogels were formulated by using different concentrations of polymers i.e. 1, 1.5, and 2%.

Evaluation of hydrogels

Physical evaluation

Table No. 7: Physical evaluations of hydrogel formulations

Formulation code	Color	Odor	Phase separation
FF1	White	Odorless	No
FF2	White	Odorless	No
FF3	White	Odorless	No

Table No. 8: Viscosity of hydrogel formulations, pH and drug content

Formulation code	Viscosity (PaS)	pH	Drug content
FF1	154.23	6.36	95.16
FF2	156.85	6.38	95.38
FF3	158.73	6.35	95.30

***In-vitro* drug release:**

Table No. 9: *In-vitro* release studies

Time	%CDR FF1	%CDR FF2	%CDR FF3
0	0	0	0
1	10.18	14.69	12.85
2	23.93	30.67	28.03
3	42.43	49.64	46.54
4	51.76	61.75	59.54
5	69.99	72.54	66.07
6	75.54	85.79	74.13

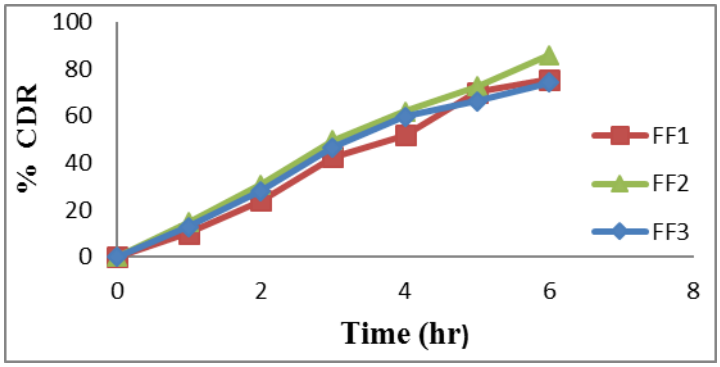

Figure No. 11: *In-vitro* release of the hydrogel formulation

In-vitro drug release study was carried out for FF1, FF2, and FF3 hydrogel formulations. The *in-vitro* release studies state the increase in the concentration of polymer decrease the drug release. The FF2 formulation showed a good release of 85.79 in 6 hrs.

Kinetic studies

Table No. 10: Kinetics release study of microemulsion emulsion formulations

Formulation Code	Zero Order	First Order	Higuchi	Peppas Plot	n- Value	Best fit model
F1	0.982	0.937	0.854	0.958	0.995	Zero order Peppas
F2	0.994	0.972	0.905	0.983	0.899	Zero order Peppas
F3	0.987	0.952	0.847	0.993	1.213	Zero order Peppas
F4	0.986	0.956	0.853	0.996	1.230	Zero order Peppas
F5	0.992	0.978	0.943	0.995	0.873	Zero order Peppas
F6	0.980	0.954	0.834	0.993	1.473	Zero order Peppas
F7	0.982	0.920	0.904	0.908	0.908	Zero order Peppas
F8	0996	0979	0.890	0.952	0.899	Zero order Peppas
F9	0994	0.964	0.889	0.998	0.982	Zero order Peppas

Table No. 11: Kinetic release studies of hydrogel formulations

Formulation Code	Zero Order	First Order	Higuchi	Peppas Plot	n- Value	Best fit model
FF1	0.986	0.966	0.900	0.990	1.144	Zero order Peppas
FF2	0.993	0.954	0.932	0.993	0.993	Zero order Peppas
FF3	0.977	0.991	0.935	0.982	0.982	Zero order Peppas

The microemulsion and MBH were subjected to drug release kinetics. The release kinetics was evaluated by zero-order and first-order equations. The mechanism of drug release was calculated by fitting the dissolution data in different models like Higuchi's and Korsmeyer-

Peppas. The results indicated the drug release from the microemulsion and MBH follows a zero-order Korsmeyer-Peppas model since regression coefficient values were higher.

CONCLUSION:

The microemulsion based hydrogel of tolnaftate was formulated to improve the topical absorption of the drug. In the current work, an attempt was made to formulate and evaluate microemulsion based hydrogel for topical delivery using oleic acid, Tween 80 and PEG 400 to impart viscosity and sustain the action. The Microemulsions were prepared by the phase titration method. The microemulsion was characterized for particle size, viscosity, drug content, % transmittance, dilution potential, thermodynamic stability testing, zeta potential, and *in-vitro* drug release studies. To the best formulation, different concentration of HPC was added to gel hydrogel, the hydrogel formulations were characterized for physical evaluation, viscosity, pH, drug content, spreadability, *in-vitro* drug release, kinetic studies. From the above studies, it was concluded that the MBH formulation can be used as a possible alternative to traditional topical formulations of tolnaftate for the therapy of fungal diseases, with improved solubility and controlled drug delivery.

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