Research Article

Formulation Development and Evaluation of Terbinafine Emulgel

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ABSTRACT

Terbinafine is a broad-spectrum antifungal drug. The aim of the research was to develop and describe a Terbinafine emulgel using Carbopol 934 and HPMC K15M as a gelling agent. By avoiding the first pass metabolism, the objective behind the formulation was to avoid dosing frequency and to increase the stability and bioavailability. All the excipients were tested for compatibility study with drug, which revealed that there was no physical and chemical interaction occurred. The physicochemical properties of the developed emulgels were evaluated, such as colour, homogeneity, consistency, spreadability, pH value, rheological behaviour, drug content, drug release, and stability. The stability and particle size are being determined by zeta potential. In-vitro drug release permeation research studies using Franz-Diffusion cell. Carbopol 934 based emulgel formulations showed highest drug release in comparison with corresponding HPMC K15M based formulations. The highest drug release 89.97%was found in formulations of F7, which follows non-fickian mechanism. Study concludes that of Terbinafine can be delivered effectively by emulgel formulations.

Keywords: Emulgel, Franz-diffusion, Terbinafine, Spreadability, Bioavailability, First pass metabolism.

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INTRODUCTION

Emulgels may be defined as biphasic systems comprising an apolar internal phase (emulsion) within an aqueous gel base. Emulgel, a novel topical drug delivery system[1], has dual release control system[2], i.e., gel and emulsion. The emulgel system is a novel drug delivery system, particularly for hydrophobic drugs. The hydrophobic drugs are mixed in an oil phase which is later incorporated within the conventionally stable gel base. To develop Topical Formulation incorporating hydrophobic drug which is not possible by simple hydrogel i.e., only possible by formulating emulgel (emulsion + gel). Emulgel is a promising drug delivery method for the delivery of hydrophobic drugs. In recent years, there has been a huge interest in using novel polymers with complex functions as emulsifiers and thickeners because their gelling[3] capacity allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension while increasing the viscosity of the aqueous phase[4].

In fact, introducing a gelling agent to the water phase modifies a conventional emulsion into an emulgel. Various drugs are administered to the skin using both oil-in-water and water-in-oil emulsions. Emulsions seem to have a sophistication to them and may be gently cleaned off as required. They're also quite good at penetrating the skin. Thixotropic, greaseless, easily spreadable, readily removable, emollient, non-staining, water-soluble, longer shelf life, bio-friendly, translucent & appealing look are just a few of the merits of using emulgels in dermatology[5].

Emulgel has several advantages, like greaselessness, ease of spreadability, easiness of removal, emollient characteristics, and transparency. Emulgels are often used to deliver analgesics, anti-inflammatory, anti-fungal[6], and anti-acne drugs, as well as a variety of cosmetic compositions. Emulgel was created in order to improve patient compliance and bioavailability.

Terbinafine is a synthetic allylamine antifungal which is fungicidal against dermatophytes, mould fungi, and some yeasts.

MATERIALS AND METHODS

Terbinafine was a gift sample from Aurobindo pharma, Hyderabad. HPMC K15M, Carbopol 934, Light liquid paraffin, Tween 20, Span 20, Propylene glycol, Ethanol, Methyl Paraben, Propyl paraben, Glutaraldehyde.

Preparation of Standard Calibration Curve

Stock solution

100 mg Terbinafine was accurately weighed & transferred into a volumetric flask filled to 100 mL with pH 6.8 Phosphate buffer as a stock solution. The resulting solution, which was labelled as 'stock,' had a concentration of 1 mg/ml.

Determination of λmax

The standard stock solution of Terbinafine was prepared in 6.8 pH phosphate buffer as well as adhered to base on approach explained in methodology area and also scanned

by UV-Visible spectrophotometer[7] in between 200-400nm. The UV absorption spectrum of Terbinafine showed λmax at 283nm and also exact same was utilized as logical wavelength for further analysis.

Serial dilutions for standard calibration curve

The necessary dilutions of Terbinafine (5-30µg/mL) solutions were produced using this second solution. Using a double beam UV-Visible spectrophotometer, the absorbances of the above solutions were measured at their maximum (283nm). A standard graph was used to plot the concentration (on the X-axis) and absorbance (on the Y-axis).

Preparation of Terbinafine Emulgel

The formulation code was designed according to a 2^3 factorial design so total eight Terbinafine emulgel[8] formulations were prepared. The optimization in the formulation batches were made mainly based on three factors i.e., gelling agent, light liquid paraffin and emulsifying agent.

Gel preparation

- The Carbopol gel was prepared by dispersing 0.25g of Carbopol 934 in purified water and soaked it overnight with constant stirring at a moderate speed. The gel was obtained by neutralizing the dispersion with tri ethanol amine and pH is adjusted to 6.5 and purified water was added to adjust the weight to 50ml.
- In case of Hydroxy Propyl Methyl cellulose gel was prepared by dispersing HPMC in hot purified water (80^0C) and the dispersion was cooled, then weight was adjusted to 50ml with purified water.

Emulsion preparation

- The oil phase of emulsion was prepared by dissolving span 20 in light liquid paraffin and heated up to 70^0-80^0C.
- Tween 20 and drug was dissolved in 5ml ethanol and heated to 700-800^0C to form an aqueous phase. Methylparaben, propylparaben were mixed in propylene glycol and glutaraldehyde and this added mixture was dissolved in aqueous phase.
- Then oil phase was mixed slowly with aqueous phase and final volume is made with purified water.
- The obtained emulsion was mixed with the gel, the volume was adjusted to 50ml with water, and the Terbinafine emulgel (w/v) was subjected to homogenization for 45 minutes.

Emulgel preparation

The obtained emulsion was mixed with the gel, the volume was adjusted to 50ml with water, and the Terbinafine emulgel (w/v) was homogenization for 45 minutes. The final formulation code of emulgel was shown in the Table-1.

Table 1: Final Formulation Code

Ingredients (% w/v)	F1	F2	F3	F4	F5	F6	F7	F8
Terbinafine (mg)	500	500	500	500	500	500	500	500
HPMC K15	0.5	0.5	0.5	0.5	-	-	-	-
Carbopol 934	-	-	-	-	0.25	0.25	0.25	0.25
Light liquid paraffin	2.5	3.75	2.5	3.75	2.5	3.75	2.5	3.75
Tween 20	0.3	0.3	0.5	0.5	0.3	0.3	0.5	0.5
Span 20	0.45	0.45	0.75	0.75	0.45	0.45	0.75	0.75
Propylene glycol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Ethanol	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Methylparaben	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Propylparaben	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005
Glutaraldehyde	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Purified water (q.s) ml	50	50	50	50	50	50	50	50

- **Drug content Determination**

Drug concentration in emulgel was measured by UV-Visible spectrophotometer. Terbinafine content in emulgel was measured by dissolving accurately 5ml of emulgel in 6.8pH phosphate buffer by Sonication and diluted to 10 folds prior to absorbance. Absorbance was measured at 283nm[9] using UV-Visible spectrophotometer 1700 (Shimadzu, Japan). The test was conducted in triplicate and the average % drug content was determined.

Drug content of all the solutions[10] were accomplished according to procedure stated in the approach area. Drug content of all the formulations was discovered to be in the array 97.54%-99.90% as shows in the Table-4.

- **pH Evaluation**

pH assessment of the topical formulation is more important as it may create inflammation to the skin if differed from regular skin pH problems. Furthermore, the polymer like Carbopol offers uniformity if the pH was

around 6. So, all the formulations were examined for the pH.

pH evaluation is an important criterion especially for topical formulations. The pH of emulgel should be in between 5-7 to mimic the skin conditions[12]. If the pH of prepared emulgel is acidic or basic, it may cause irritation to the patient.

- **Rheological studies**

The thickness of all the solutions were measured using Brookfield viscometer at 10 rpm utilizing spindle 6, it was found that all the formulas were adhered to shear thinning result with thixotropic property. It was observed that as the emulsion-gel[13] ratio increases, the formulation thickness increases.

- **Spreadability test**

Spreadability is one of the parameters for a dermatological preparation to satisfy the ideal qualities. The term "spread ability" refers to the area across which the gel spreads easily when applied to the skin or the affected area.

The therapeutic efficacy of the formulation also depends on the spread ability values. Hence determination of spread ability is an important emulgel evaluation[14] parameter, spread ability is measured as:

$$S = M \times L/T$$

Where,

M = weight to be taken

L = length of the slide

T = time taken

The spreadability of each sample was evaluated in triplicate by using fabricated spreadability apparatus which consists of two glass plates. 0.5g of the sample was placed on lower plate and upper plate was placed on the top of the sample. Force was generated by adding increasing weight slowly at 1 minute interval into the pan connected to the upper plate, each sample was tested three times at constant temperature and exerted weight and the mean values of the spread surface area on lower plate were calculated.

- **Isolation of egg membrane**

Egg was taken as well as made a tiny hole on the suggestion part of the egg. The components of the egg were eliminated via that opening. Then egg shell was cleaned internally with water and also dipped into 0.1 N Hcl remedy for 4 hrs. The external covering of the egg would liquify and also egg membrane was separated from it.

- **In-vitro Drug permeation research study**

In-vitro permeation research was performed using keishary chein cell having capability of 18ml volume. Egg membrane was separated and utilized for the study. 5ml of emulgel was spread out evenly on to the egg membrane layer. The egg membrane was secured between donor and receptor area. The receptor area was loaded with 16ml of 6.8 pH phosphate barrier maintained at 37ºC and also stirred by using magnetic stirrer. The sample (2ml) was gathered at convenience intervals[11] as well as evaluated for medication material by UV-Visible Spectrophotometer 1700 (Shimadzu, Japan) at 283nm after proper dilutions as talked about previously.

RESULTS AND DISCUSSION

Identification of authenticity of Terbinafine pure drug

Physical appearance

Physical appearance of the drug was examined by organoleptic properties and results were obtained as follows:

All the formulations were evaluated for colour, homogeneity and consistency. The physical appearance of all the formulations was found to be, creamy white, homogenous and consistent.

Solubility Studies

Solubility studies of terbinafine different solvents as demonstrated in the below Table 2.

Table 2: Solubility studies

Solvents	Solubility
Water	Slightly soluble
pH6.8 Phosphate buffer	Soluble
Methanol	Soluble
Chloroform	Soluble

As per the solubility studies the drug solubility in organic solvents was higher than in water.

The IR spectrum of Terbinafine pure drug and Terbinafine optimized formulation were recorded by FTIR spectrophotometer. It showed that functional group peak frequencies of Terbinafine were in resemblance to the reported range of standard Terbinafine which authenticated that the obtained sample of Terbinafine of pure drug. FTIR spectra of Terbinafine and its optimized formulation was shown in figure 1 & 2.

Table 3: Calibration Data of Terbinafine

S. No.	Conc.(µg/ml)	Absorbance
1	0	0
2	5	0.21
3	10	0.416
4	15	0.601
5	20	0.753
6	25	0.904
7	30	1.076

FTIR Studies

Drug excipient compatibility study

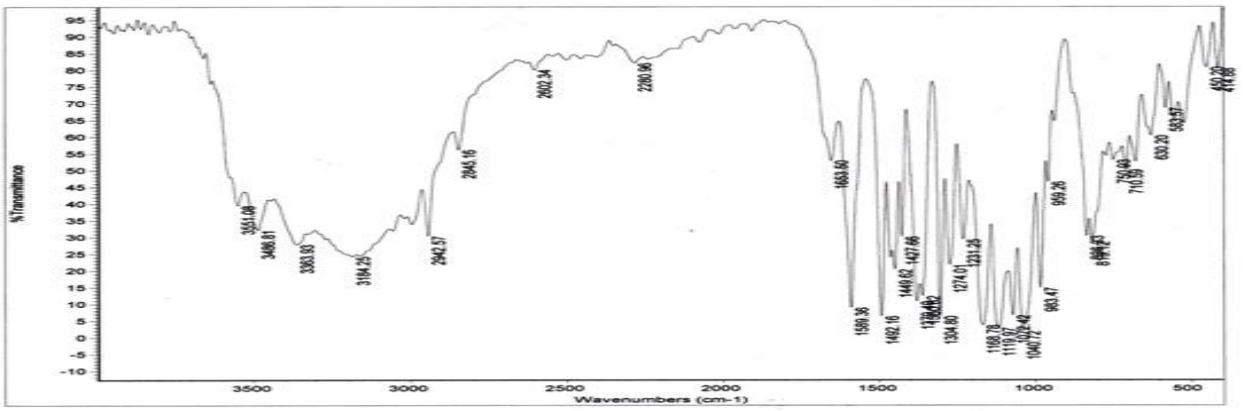

Figure 1: FTIR for Terbinafine Pure Drug

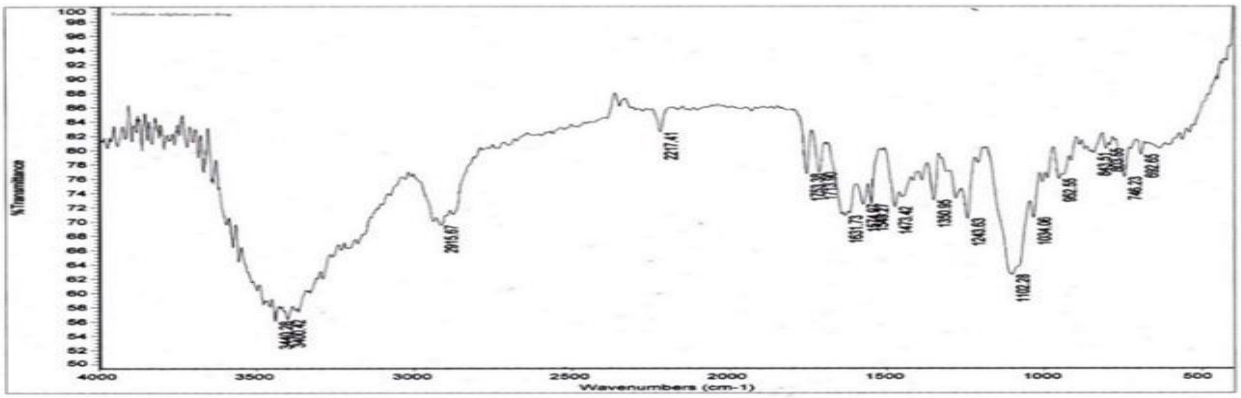

Figure 2: FTIR for Terbinafine Optimized Formulation

Calibration curve of Terbinafine

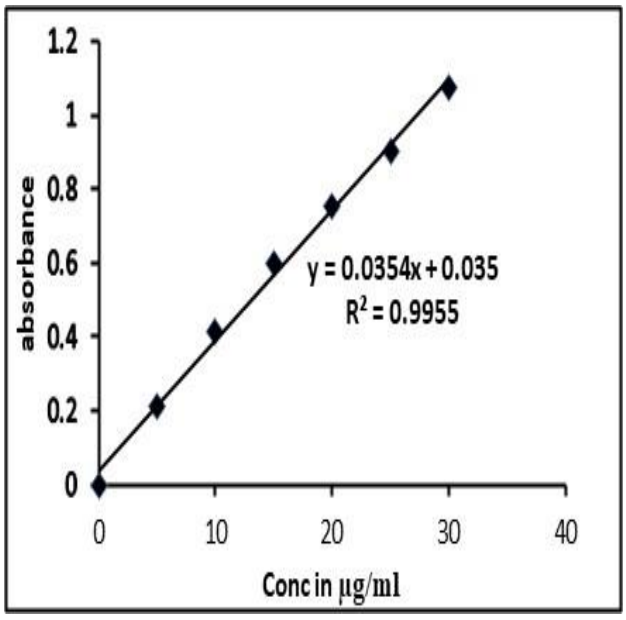

Figure 3: Calibration curve of Terbinafine

From calibration regression equation (Y=0.0354X + 0.035) and correlation coefficient (R^2 = 0.9955) Indicated that analytical method obeys Beer- lamberts law in the concentration range of 0-30µg/ml. The results were shown in the Table-3 and calibration graph of Terbinafine was shown in Figure-3.

pH Evaluation

pH evaluation of the topical formulation is more important as it may cause irritation to the skin if varied from normal skin pH conditions. Furthermore, the polymer like Carbopol gives consistency if the pH was around 6. So, all the formulations were evaluated[16] for the pH. The Data were shown in the Table-4.

Spreadability Studies

Spread ability study is one of the criteria for an emulgel to meet the ideal qualities that it should possess good spread ability. If spread ability value is more, it would be properly spread over the skin which is more beneficial as per patient compliance concern. All the formulations were checked for the spreadability[17] and the data were given in Table 4. By taking the data into consideration it was observed that concentration of span 20 and tween 20 makes the difference in the spreadability F7 were having maximum concentration of span 20 and tween 20 compared to other formulations and the spread ability values were found to be more for both formulations compared to other formulations.

Evaluation parameters

Table 4: Evaluation parameters

S.no	Formulation code	pH	Spreadability (cm/sec) *	Viscosity (cp)	Drug content (Mean%)
1	F1	6.4±0.43	3.0±0.01	3600	98.41
2	F2	6.1±0.63	3.5±0.40	3300	99.15
3	F3	6.7±0.25	3.2±0.55	3900	98.02
4	F4	6.0±0.72	3.4±0.48	3650	99.47
5	F5	6.3±0.11	3.5±0.62	4300	98.83
6	F6	6.4±0.24	4.1±0.12	3100	97.54
7	F7	6.7±0.88	2.5±0.75	4800	98.74
8	F8	6.5±0.02	2.3±0.23	3100	99.90

Rheological Study Data

All of the formulation's viscosities were measured using a Brookfield viscometer at 10 rpm with spindle 6, and it was found that they all had a shear thinning effect with thixotropic properties. It was observed that as the emulsion-gel ratio increases, the viscosity[18] of the formulation increases. The Data were shown in the Table-4.

Drug Content Determination

Drug content of all the formulations were carried out as per procedure stated in the methodology section. As shown in the Table-4, the drug content of all formulations was found to be in the range of 97.54 % to 99.90 %.

***In-Vitro* Drug Permeation Data**

Table 5: % cumulative drug release data for F1 to F8 & Marketed gel

Time (hrs.)	% Cumulative drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	Marketed gel
0	0	0	0	0	0	0	0	0	0
1	5.17	5.56	4.10	5.18	6.01	3.94	8.80	5.76	7.23
2	12.02	8.61	7.25	7.93	13.42	6.15	16.51	7.51	14.56
3	16.54	13.25	10.93	12.45	25.08	9.37	29.72	11.05	22.54
4	25.16	19.13	12.28	17.62	32.75	11.20	38.64	16.54	32.65
5	33.47	26.58	23.68	26.01	38.62	22.46	47.38	25.93	45.23
6	41.31	34.40	28.41	32.85	45.27	25.34	55.13	30.24	51.66
7	49.67	42.79	33.06	42.56	56.91	29.81	63.02	38.85	60.89
8	58.46	49.83	37.12	46.42	62.84	34.65	70.61	40.69	68.23
9	60.02	52.32	42.62	49.83	68.56	40.65	77.54	45.65	72.56
10	68.32	59.82	49.53	52.64	76.85	46.74	83.45	52.25	79.57
11	74.60	63.25	53.62	57.45	80.25	50.15	85.05	55.48	81.19
12	76.77	69.53	60.31	62.06	84.32	58.09	89.97	63.42	86.23

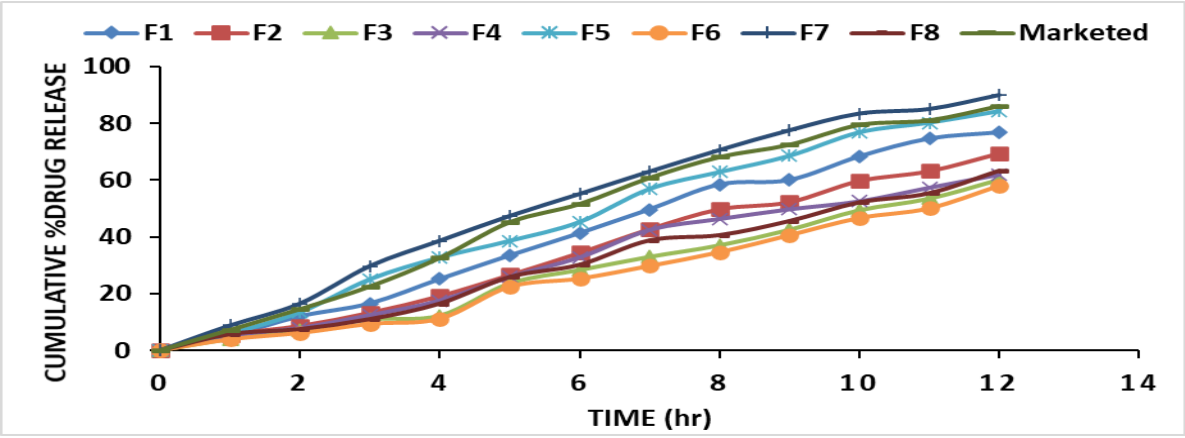

Figure 4: *In vitro* drug permeation graph

The in-vitro permeation studies of all the formulations were carried out using Keishary chein as described in the methodology[19] section using egg membrane as a permeation membrane for the study. The comparative cumulative percentage drug permeation data of all the formulations F1 to F8 were shown in the Table-5 and plots in the Figure-4 respectively.

The optimized formulation F7 containing maximum concentration of span 20 and tween 20 showed highest % drug[20]permeation at the end of 12 hrs and hence this formulation was selected as optimized formulation for further study. It was revealed that span 20 and tween 20 concentration was having positive effect on the drug permeation through the membrane.

The drug release kinetics was studied with invitro drug permeation[21]data for all the formulations F1 to F8. As a model dependent approach, the dissolution data was fitted into release models such as Zero order, first order, Higuchi, Peppas Model to understand the order and mechanism of Terbinafine release from emulgel and results were stated in the Table-6 & Figure were shown in 5, 6, 7, 8. The Best fit model for selected formulation F7 were found to be Zero order model with non-fickian diffusion.

Drug release kinetics:

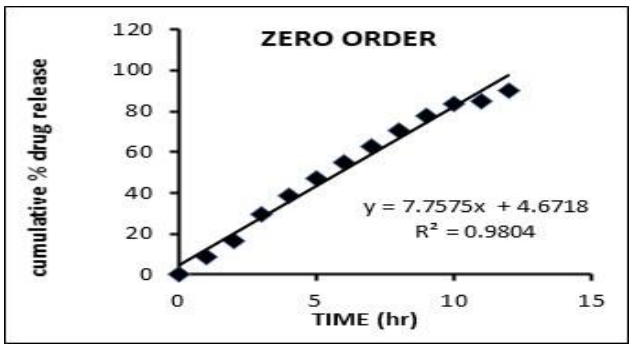

Figure 5: Zero order graph of optimized F7 formulation

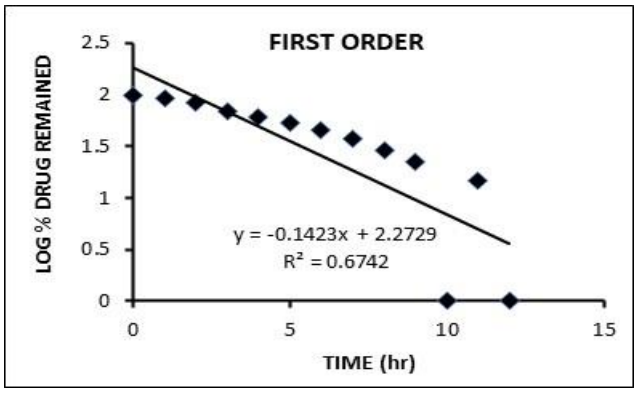

Figure 6: First order graph of optimized F7 formulation

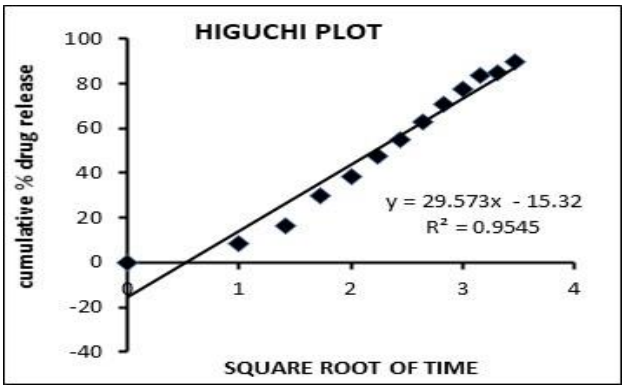

Figure 7: Higuchi graph of optimized F7 formulation

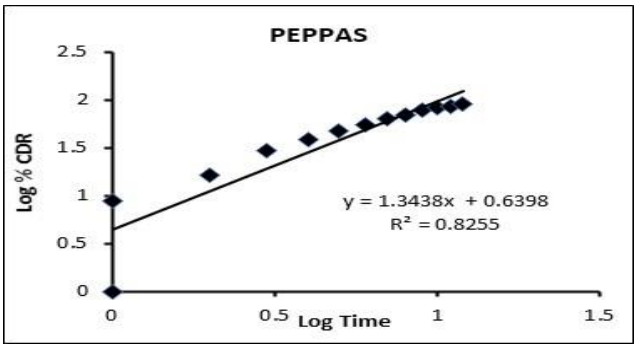

Figure 8: Peppa's graph optimized F7 formulation

Table 6: Release kinetics of optimized formulation

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	7.757527473	-0.14226443	29.57298225	1.343816675
Correlation	0.990176129	-0.82109574	0.976979985	0.908588553
R 2	0.980448767	0.674198227	0.95448989	0.825533159

Scanning electron microscope study

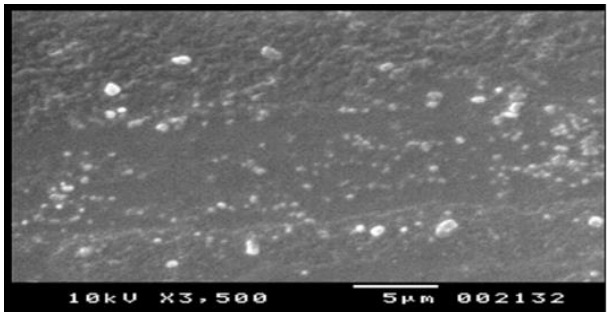

Figure 9: SEM of Best formulation (F7)

Scanning electron microscopy was performed to study the surface characteristics of emulgel was shown in Figure-9.

CONCLUSION

Terbinafine is categorized as artificial allylamine antifungal drug. The purpose of this study was to develop the most effective topical preparation for avoiding terbinafine first-pass metabolism in the treatment of antifungal infections with maximum drug release and reduce g.i.t adverse effects. Terbinafine maximum wavelength is figured out by UV-Visible spectrophotometer utilizing 6.8 pH phosphate buffer and was found to be 283 nm. Terbinafine emulgel

was formulated utilizing light liquid paraffin as oil phase as well as emulsifying representative's tween 20 and also span 20 for emulsion as well as included right into gel making use of HPMC as well as Carbopol 934 polymers in various ratios. The optimized formulation(F7) of Emulgel showed the highest drug release, appropriate spreadability, good consistency and higher percentage inhibition. In the study it was observed that the concentrations of tween20, span 20 and also light liquid paraffin has actually revealed effect on viscosity, spreadability and in-vitro drug permeation. Enhanced amount of liquid paraffin showed subdue task of tween 20 as well as span 20. Thus, Terbinafine emulgel which could boost the drug permeability across the skin and also fast release of the drug could be successfully attained. On the basis of performed experimental work, it is concluded that the nature of the polymers used in preparation of gels and their concentrations showed an effect on the release of Terbinafine from emulgel base. Among gelling agents, Carbopol 934 form more viscous gels than HPMC K15M.Carbapol has more viscosity than HPMC. Therefore, it can be concluded that Terbinafine being hydrophobic in nature and is established drug could be a promising topical alternative for the treatment of skin infections and achieving controlled release with enhanced bioavailability and drug targeting to affected sites.

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