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Original Research Paper

FORMULATION AND EVALUATION OF TERBINAFINE HYDROCHLORIDE FILM FORMING EMULGEL

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ABSTRACT

The purpose of present research work was to develop a Film Forming Emulgel formulation of Terbinafine hydrochloride using carbopol 934 as a gelling agent for topical delivery with the aim to avoid hepatic first-pass metabolism, improve stability of emulsion, reduce dosage regimen and enhance residence time in the treatment of fungal infection. Film Forming Emulgels have emerged as one of the most interesting topical drug delivery systems as it has dual release control i.e. emulsion and gel. The developed emulgels were evaluated for their physicochemical properties like color, homogeneity, consistency, spreadability, pH value, rheological behavior, drug content, drug release and stability. Commercially available Terbinafine hydrochloride cream was used for comparison. All the prepared emulgels showed satisfactory physicochemical properties like color, homogeneity, consistency, spreadability, and pH value. The drug release was found to be higher for optimized formulation as compared to the marketed Terbinafine hydrochloride cream. The highest drug release was observed with T4, where the drug release showed 92.05%. The drug release from all the emulgels were found to follow diffusion-controlled mechanism. Stability studies indicated that the physical appearance, rheological properties, spreadability, drug release in all the prepared emulgels remained unchanged upon storage for 3 months.

Keywords: Terbinafine hydrochloride, Carbapol 934, Antifungal activity, Film formation, Emulgel formulation.

INTRODUCTION

Film Forming Emulgels are emulsions, either of the oil-in-water or water- in- oil type, which are gelled by mixing with a gelling agent. They have a high patient acceptability since they possess the previously mentioned advantages of both emulsions and gels. Therefore, they have been recently used as vehicles to deliver various drugs to the skin. Film Forming Emulgel is stable one and better vehicle for hydrophobic or water insoluble drugs. Terbinafine Hydrochloride is an allylamine which has a broad spectrum of antifungal activity in fungal infections of the hair and skin such as Pityriasis versicolor. It shows oral bioavailability is about 40% because of first pass hepatic metabolism. So Terbinafine is increasingly administered by topical route may increase the bioavailability. Terbinafine is very slightly soluble in water so because of its hydrophobicity, emulsion can formulate. Emulsion is used both for hydrophilic and hydrophobic drug but stability is the major problem in case of emulsion. When gel incorporated in an emulsion can be overcome the stability problem of emulsion. Gel is having good absorption property along with greaseless, easily spreadability, easily removable, nonstaining and emollient but major limitation is delivering hydrophobic drug. The aim of present work was to develop an emulgel (combination of emulsion and gel) formulation of Terbinafine hydrochloride by using carbopol as a gelling agent. Emulgel has dual release mechanism due to emulsion & gel.

About Fungal Diseases

Superficial infections are confined to skin, hair, nails or mucous membranes. The most common fungal skin infections are the dermatophytoses, pityriasisversicolor, and candidiasis. Approximately 90% of fungal skin infections are caused by 'dermatophytes', which are parasitic fungi affecting the skin, hair, nails.

- One of the leading antifungal agents for topical treatment of fungal infections is terbinafine Hydrochloride. It has been approved by the US Food and Drug Administration in cream, gel, solution and spray dosage forms.
- Terbinafine Hydrochloride is an allylamine antifungal agent widely utilized in the treatment of infections caused by dermatophytes. It is also reported to have good activity in vitro against *Cryptococcus*, some species of *Candida*, *Penicillium marneffei*, *Aspergillus*, and other filamentous fungi.
- The mode of action for terbinafine Hydrochloride involves inhibition of enzyme squaleneepoxidase in fungal ergosterol biosynthesis, which induces accumulation of intracellular squalene and cellsdeath. Topical therapy is an attractive choice for the treatment of the cutaneous infections due to its advantages such as targeting of drugs to the site of infection and reduction of the risk of systemic side effects.
- Systemic treatment is usually reserved for infections of the nails, extensive cutaneous infections or those which have not responded to topical therapy. Conventional topical formulations are unable to retain the drug over the skin for a prolonged period and hence necessitate longer treatment duration or have to be supplemented by oral therapy.
- For effective local delivery of an antifungal that is applied to the surface of the skin, the agent must be partitioned firstly from the vehicle into the stratum corneum, and then partitioned to the local tissues including the viable epidermis, dermis, subcutaneous tissue and appendages.
- The need for multiple applications a day is frequently associated with poor compliance of patients. Thus, prolonging the contact time of active substances to the skin and thereby reducing the application frequency is subject of intensive research.
- Sustained release delivery systems with features of both semisolid formulations and patches may be employed here. The concept of film forming formulations is very recent. Film forming formulations may be solutions, gels or emulsions. Film forming formulations are defined as non-solid dosage forms that produce a substantial film in situ after application on the skin or any other body surface. Such compositions can either be liquids or semisolids with a film forming polymer as basic material for the matrix. The formed film is sufficiently substantial to provide a sustained drug release to the skin.
- Very few examples of film forming gel formulations have been reported in literature. BeeGentleTM and GELNIQUE are commercially available film forming gel formulations.

MATERIAL AND METHOD

Terbinafine hydrochloride (Macleods Pharmaceuticals Pvt. Ltd, Baddi), Carbapol 934 (Rajesh Chemical Co. Mumbai), Liq. Paraffin (M/S Yarrow Chem. Product Mumbai), Propylene Glycol (M/S Engineering Project & Cables Pune), Ethanol (Rajesh Chemical co. Mumbai), Eudragit RSPO M/S (Balaji Drugs Surat), Hydroxy Propyl Cellulose (Macleods Pharmaceuticals, Baddi).

Emulgel Preparation

The Gel in formulations were prepared by dispersing Carbopol 934 in purified Water with constant stirring at a moderate speed and Carbopol 940 in purified water with constant Stirring at a moderate speed then the pH are adjusted to 6 to 6.5 using Tri ethanol amine (TEA). The oil phase of the emulsion were prepared by dissolving Propylene Glycol in light liquid paraffin, while the aqueous phase was prepared by dissolving Drug in ethanol.

Method of Preparation

Step-1: Formulation of Emulsion either O/W or W/O
Step-2: Formulation of gel base
Step-3: Incorporation of emulsion into gel base with continuous stirring
Step-4: After formulation of emulgel addition of film forming solution
The flow chart of emulgel preparation is shown in figure

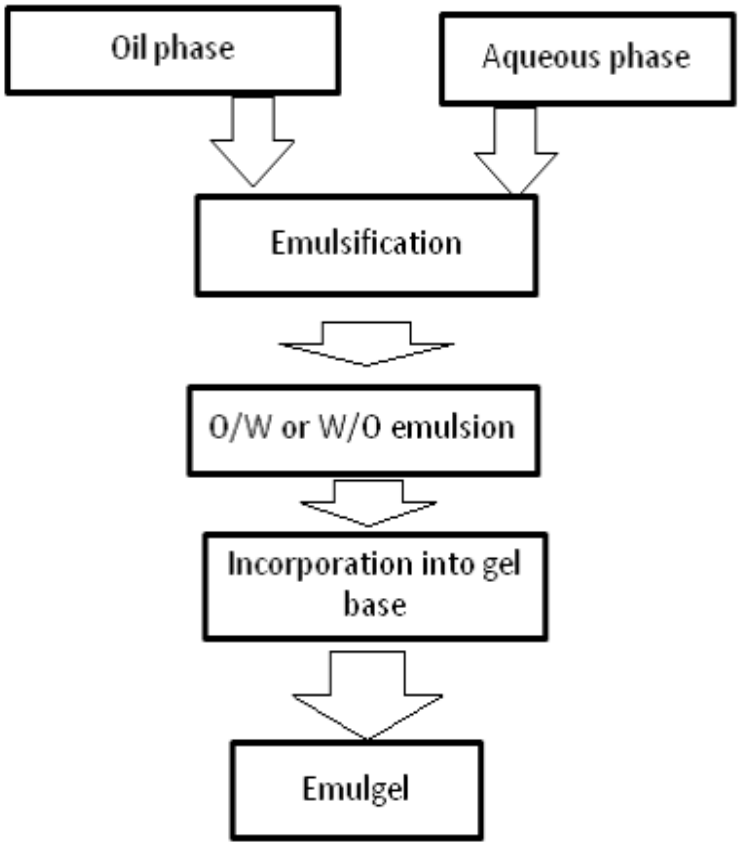

Figure 1: Flow Chart of emulgel formulation.

Table 1: Formulation design

Ingredient	T1	T2	T3	T4
Terbinafine Hydrochloride (%w/v)	1.0	1.0	1.0	1.0
Carbapol934 (%w/v)	1.0	1.0	1.0	1.0
Liq. paraffin (%w/v)	6.0	6.0	8.0	8.0
Propylene Glycol (%w/v)	5.0	5.0	5.0	5.0
Ethanol (%w/v)	5.0	5.0	5.0	5.0
Eudragit RSPO (%w/v)	12.5	12.5	20.0	20.0
Hydroxypropyl Cellulose(%w/v)	6.0	10.0	6.0	10.0
Purified Water	q.s	q.s	q.s	q.s

RESULT AND DISCUSSION

Analytical Profile

The sample of Terbinafine Hydrochloride procured for study was identified by Infrared spectrum, Differential Scanning Calorimetry.

Determination of analytical wavelength

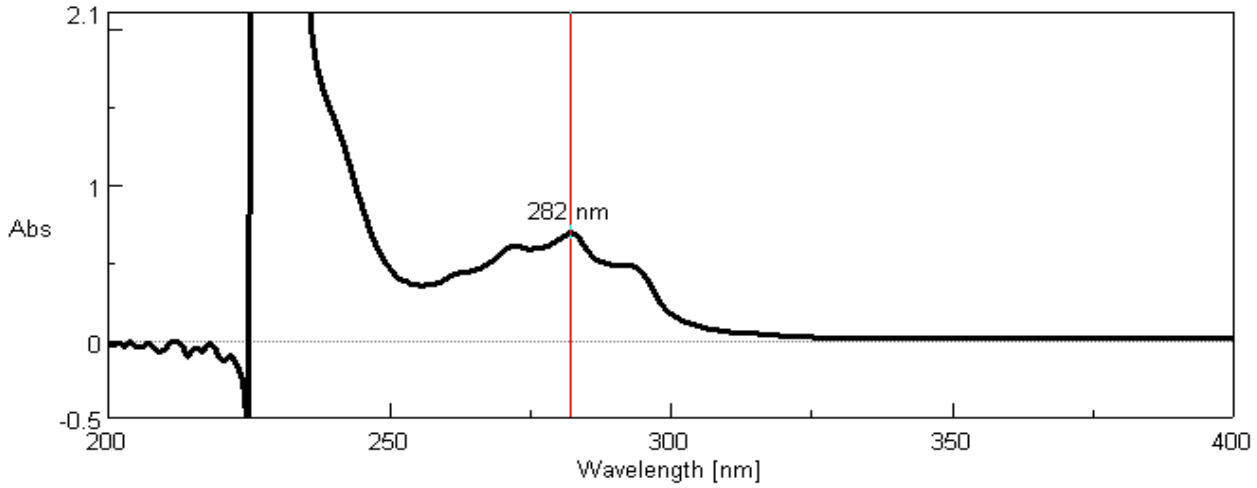

Figure 2: U.V. Spectrum of Terbinafine Hydrochloride

Calibration Curve of Terbinafine Hydrochloride

The standard calibration curve of Terbinafine Hydrochloride was obtained by plotting Absorbance vs. Concentration. Table shows the absorbance values of Terbinafine Hydrochloride. The standard curve is shown in figure. The standard calibration curve shows the slope of and 23.66 correlation coefficient of 0.9998. The curve was found to be linear in the concentration range of 5-30g/ml (Beer's range) at 282 nm. The calculations of drug content, in vitro dissolution study were based on this calibration curve.

Table 2: Analytical data for calibration curve of terbinafine hydrochloride

Sr. No.	Concentration	Absorbance
1.	5	0.1684
2.	10	0.3733
3.	15	0.5836
4.	20	0.8125
5.	25	1.0158
6	30	1.2154

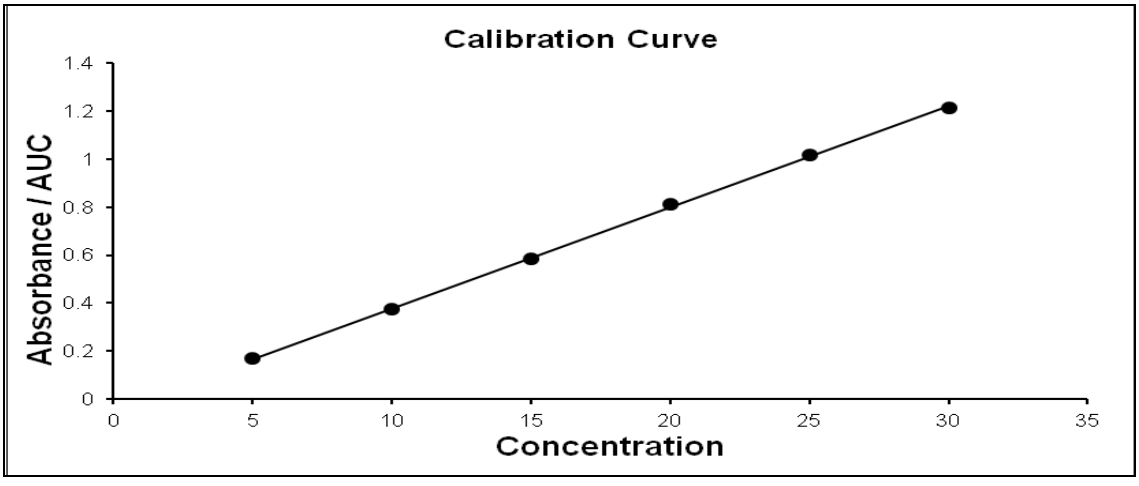

Figure 3: Calibretion Curve of Terbinafine Hydrochloride

Table 3: Data for calibration curve in pH 6.1 phosphate buffer solution

Sr. No.	Parameters	Values in pH 6.1 phosphate buffer
1.	Absorbance maximum (λ_{max}) in nm	282nm
2.	Slope	0.06
3.	Intercept	0.0173
4.	Correlation coefficient	0.999
5.	Equation	y = 0.042x - 0.044

Melting Point Determination

Melting point of Terbinafine Hydrochloride was found to be 205˚C as reported in literature, thus indicating purity of sample.

Evaluation of Terbinafine Hydrochloride Film Forming Emulgel

Table 4: Drug Content, Viscosity, Spreadability and Swelling index of prepared Formulation

Formulation	Drug content (%w/w)	Viscosity of Emulgel Formulation (Pa.S)	Spreadability	Swelling index
T1	81.00%	1.432	71%	17%
T2	88.93%	1.521	80%	20%
T3	85.83%	1.524	79%	19%
T4	92.21%	3.771	85%	21%

Table 5: Physical examination

Sr. No.	Formulation code	Colour	Phase separation
1	T1	White	None
2	T2	White	None
3	T3	White	None
4	T4	White	None

pH Determination

The pH of the emulgel formulation was in the range of 5.5 to 6.5.which lies in the normal pH range of the skin and would not produce any skin irritation. There was no significant change in pH value as function of time for all formulation.

Table 6: pH Determination

Sr. No.	Formulation code	pH
1	T1	5.8
2	T2	6.1
3	T3	6.0
4	T4	6.1

Table 7: In vitro release profile of drug prepared formulation

Cumulative Percentage Drug release

Sr.No.	Time	T1	T2	T3	T4
1	0	0.000	0	0	0
2	10	2.563	2.8	3.2	4.21
3	20	3.123	7.91	8.71	12.25
4	30	5.123	11.13	13.21	16.25
5	40	9.125	15.91	17.35	23.12
6	50	16.235	23.17	24.31	29.124
7	60	22.145	28.22	29.33	34.78
8	70	27.456	33.93	35.12	40.123
9	80	33.125	41.37	43.57	48.123
10	90	38.450	47.452	53.46	55.85
11	100	42.110	52.456	60.98	62.123
12	110	49.258	61.123	70.74	82.54
13	120	60.142	75.123	85.65	91.00

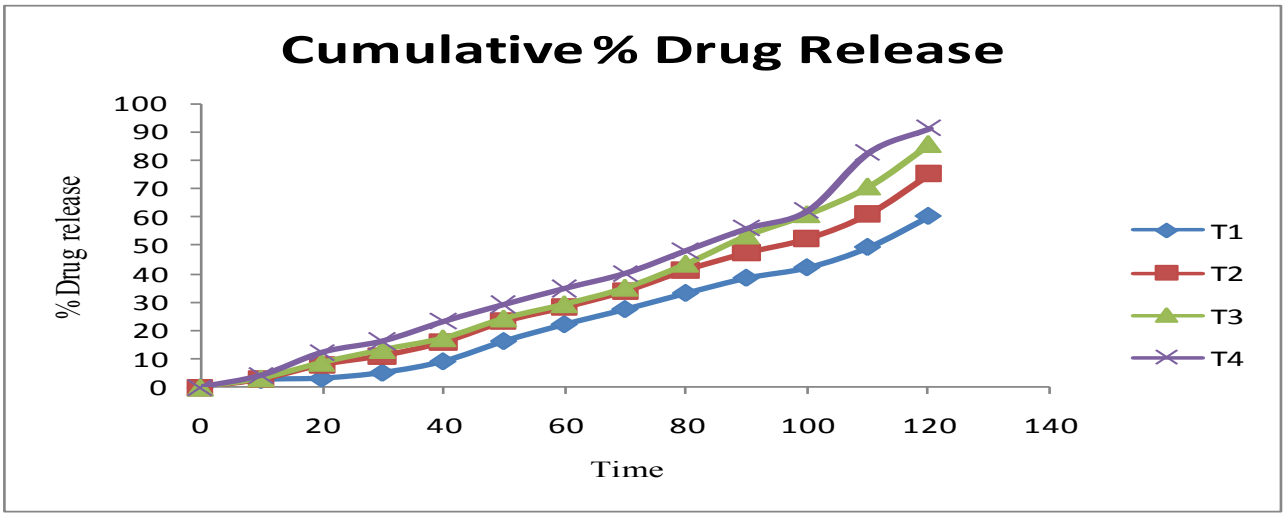

Figure 4: 7.3 % Cumulative Drug Release

IR spectroscopy analysis

Table 8: IR spectroscopy analysis

Absorption peak	Attributed to
2949.16	C-H
758.02	CL-
1737.86	C=O
1319.31	C-N

[(E)-N, 6, 6-trimethyl-N-(napthalen-1-methyl) hept-2-en-4yn-1-amine; hydrochloride]

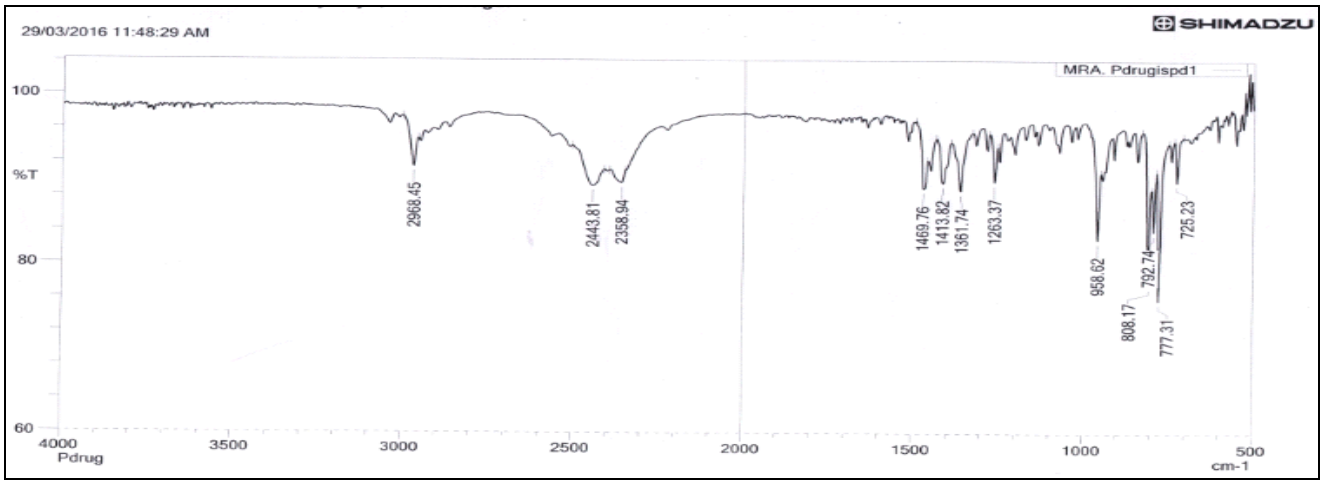

Figure 5: IR Spectra of Terbinafine Hydrochloride (Plain drug)

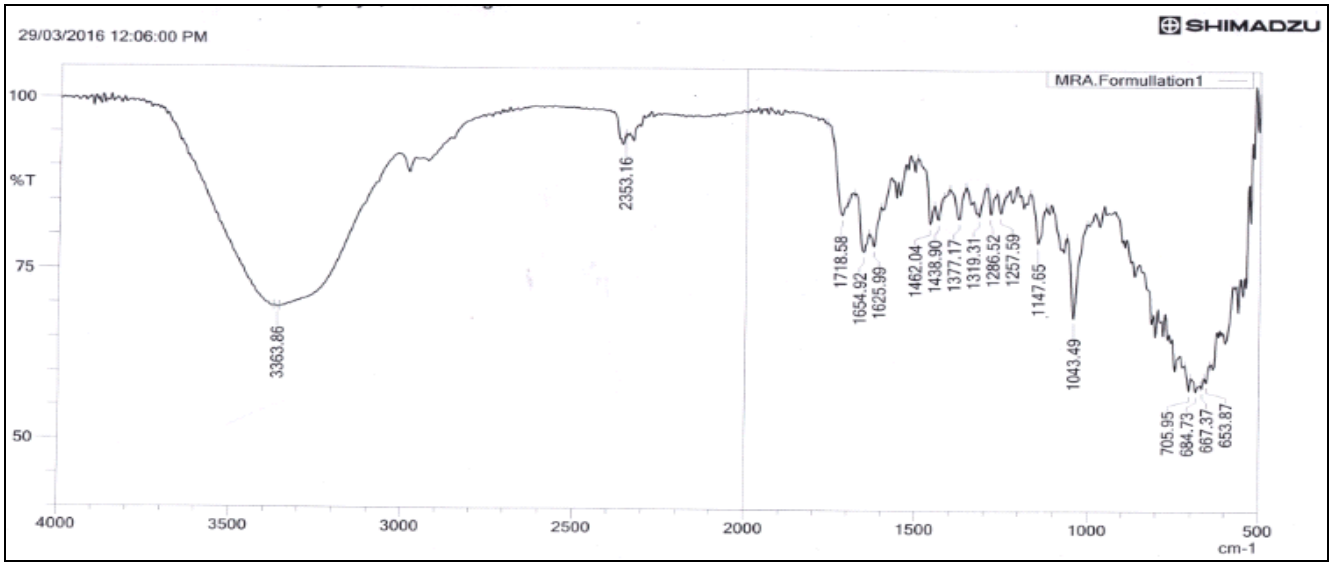

Figure 6: IR Spectra of Formulation

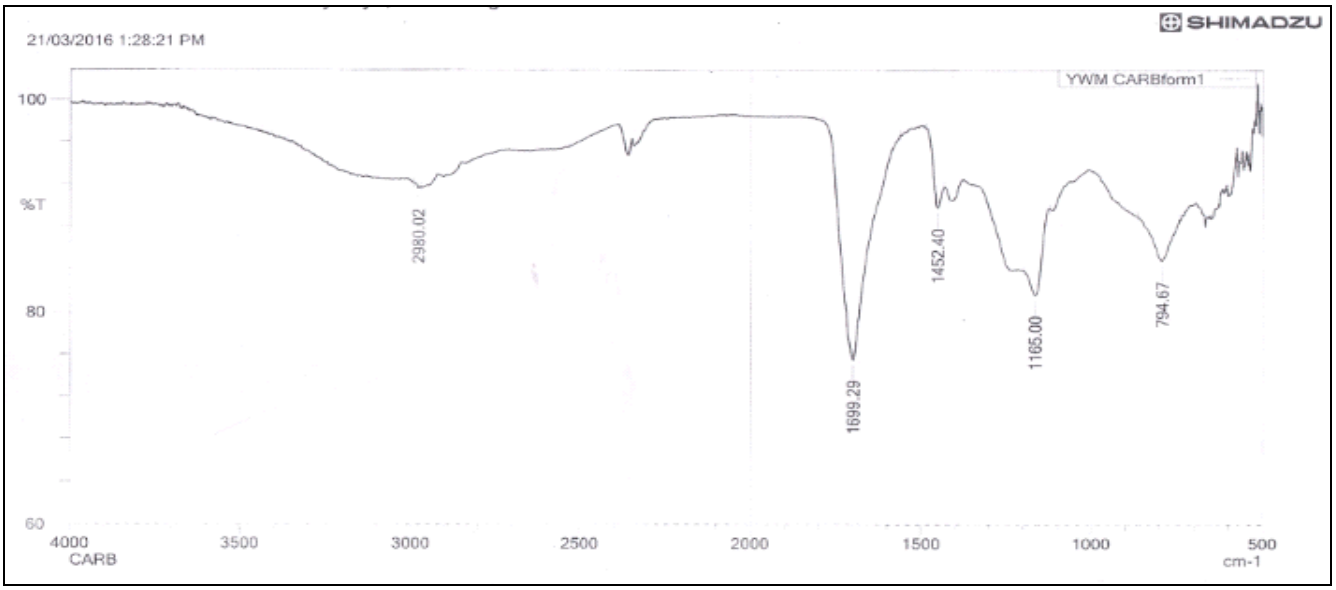

Figure 7: IR Spectra of carbapol

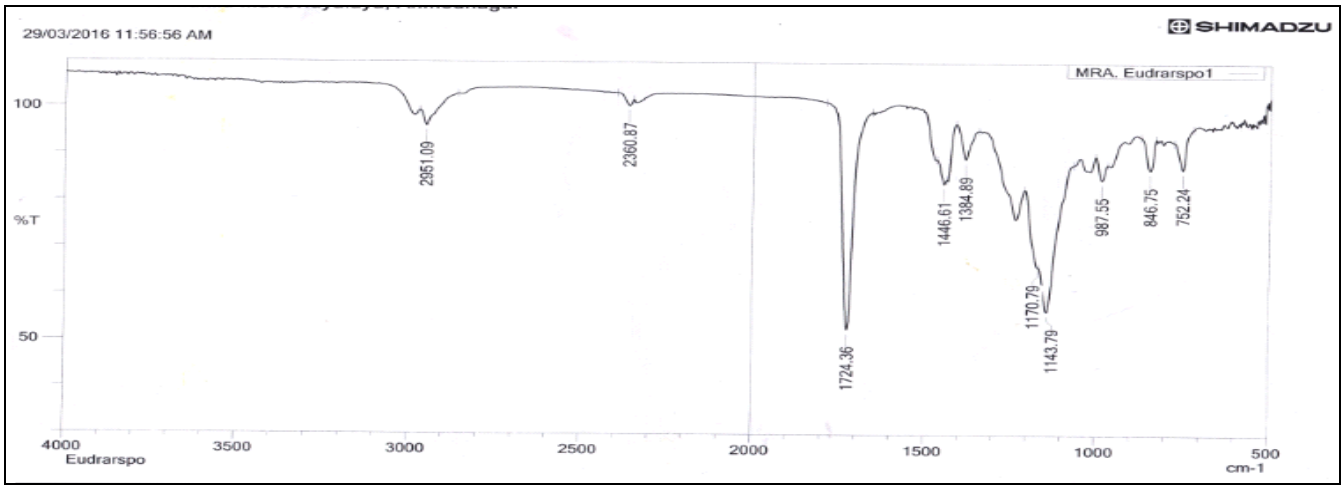

Figure 8: IR Spectra of Eudragit RSPO

Differential Scanning Calorimetric Analysis

The exothermic peak of Terbinafine Hydrochloride was seen at 207˚C with an onset 208˚C, formulation was seen at 210 ^{0}C . This complies with the reported literature value.

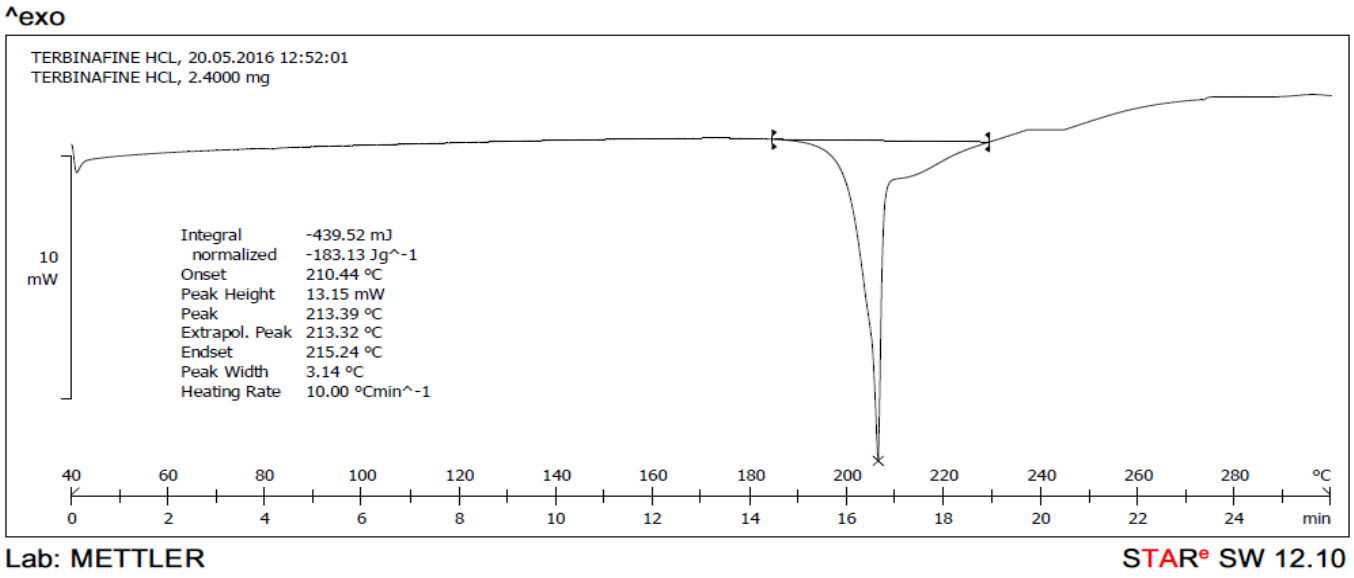

Figure 9: Thermogram of Terbinafine Hydrochloride

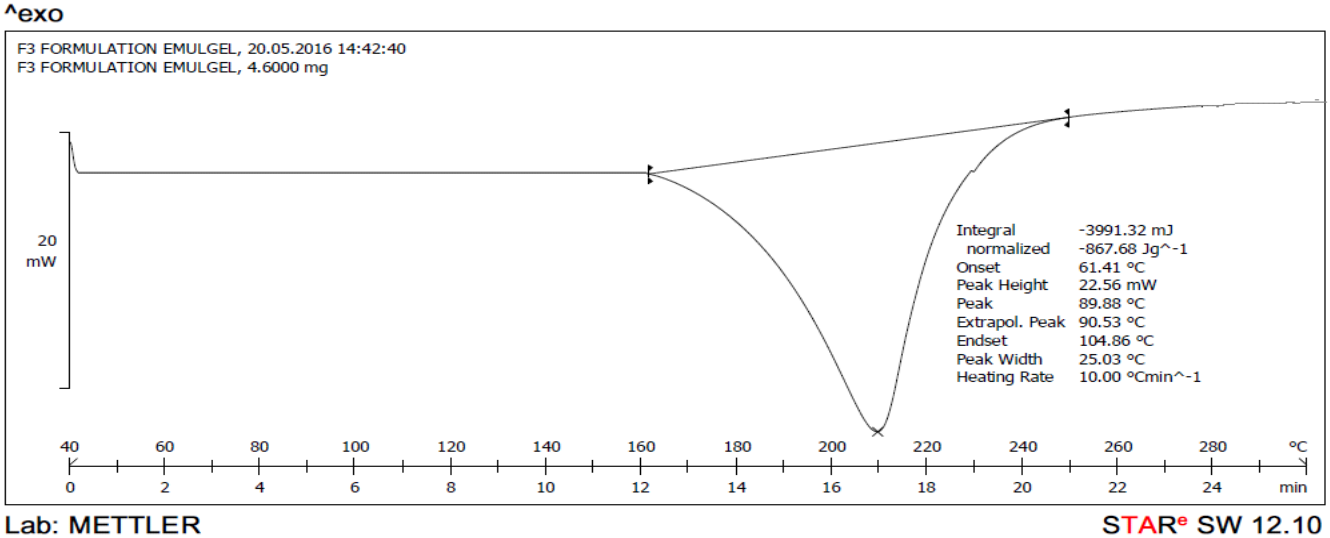

Figure 10: Thermogram of Formulation

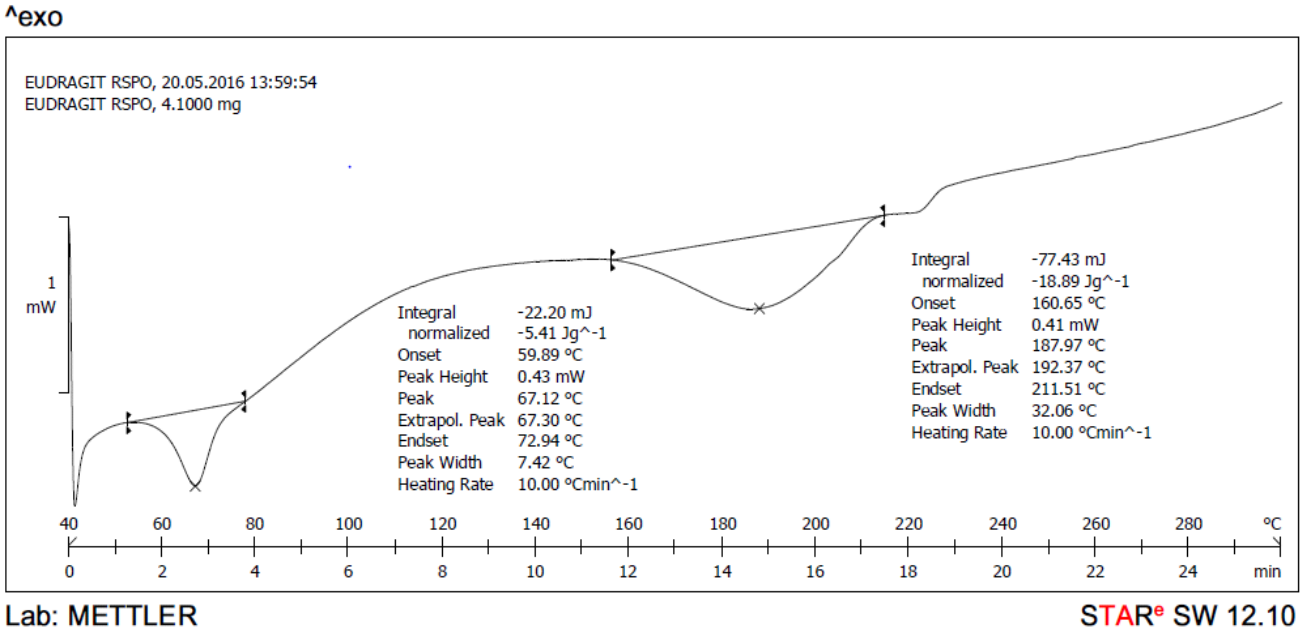

Figure 11: Thermogram of Eudragit RSPO

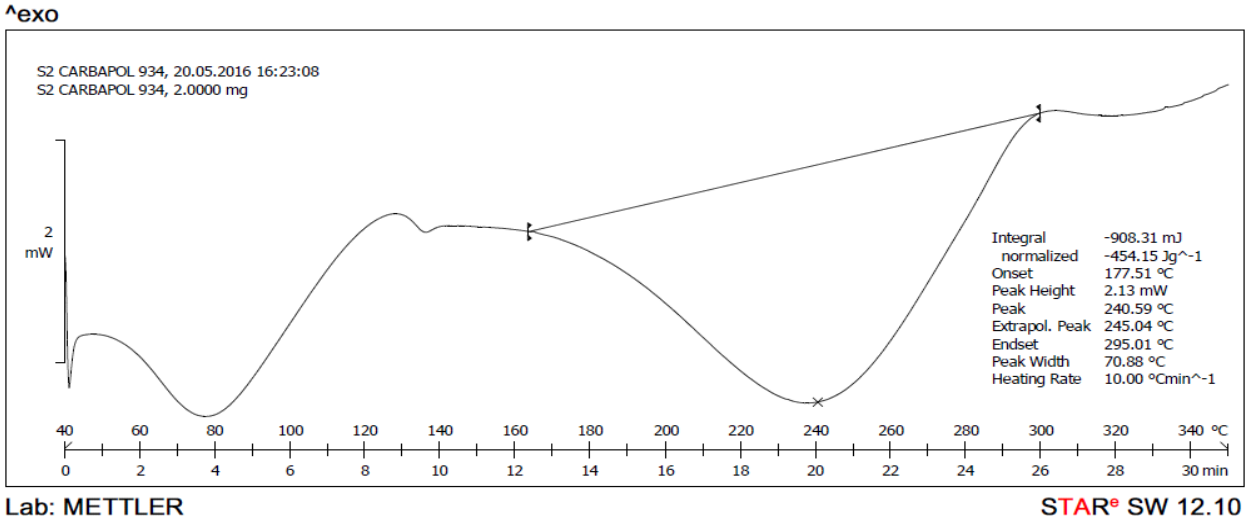

Figure 12: Thermogram of Carbapol 934

Figure 13: Photographs of diffusion study of egg membrane

Microbiological Assays

Percentage inhibition was taken as a measure of antifungal activity. The heigst activity was observed with T4 Where percentage inhibition found to be 63.

Table 9: Microbiological assays

Sr.No.	Formulation	MIC[%]$_t$ SD
1	T1	53
2	T2	57
3	T3	54
4	T4	63

Accelerated Stability Studies of the Optimized Formulation

The samples (in triplicate) of best formulation kept sealed and exposed to controlled temperature (40±2 °C) and relative humidity (75±5 %) for a period of 45 days in stability chambers (Thermolab Scientific Equipment Pvt. Ltd.). After 30 and 45 days, samples were taken out and analyzed for the following tests:

Table 10: Stability parameters of 3 month

Formulation	Study conditions specification	Month	Viscosity	Drug Content (%w/w)
T4	40^0c ± Initial 2^0c/75% ± 5% RH	Month 1	33.08	92.21%
		Month 2	34.14	92.11%
		Month 3	35.09	92.7%

CONCLUSION

Conclusion-from above study following conclusion can be made:

- Film forming Emulgel of Terbinafine Hydrochloride was prepared using Eudragit RS PO and hydroxyl propyl cellulose.
- Antifungal study showed that developed film forming Emulgel can reduce the fungal burden and thus, is more effective product.
- The film forming dermal Emulgel prepared in this study fulfills all necessary parameters required for topical use. This novel dosage form will improve both the accuracy and the positioning of a delivered dose.
- The optimized batch (T4) of Emulgel showed the highest drug release, appropriate spreadability, good consistency and higher percentage inhibition.
- Hence, the results of the present study clearly indicated promising potentials of film forming Emulgel as topically in the treatment of fungal infection and could be viewed as a potential alternative to conventional dosage forms.

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