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FORMULATION DEVELOPMENT AND EVALUATION OF TOPICAL NANOEMULGEL OF NAFTIFINE HYDROCHLORIDE

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ABSTRACT

The objective of this study was to develop a Naftifine Hydrochloride (2 % w/w) formulation in the form of a nanoemulsion-based emulgel. The nanoemulsion was prepared using high-speed homogenization and evaluated for various physicochemical properties. Emulsion instability issues were addressed by formulating a drug-loaded Nanoemulgel using a 32 full factorial design, with almond oil concentration and homogenization speed (rpm) as independent variables, each at three levels. Prior to formulation, preformulation studies were conducted to assess the drug's purity, compatibility with excipients, and physicochemical characteristics. These included organoleptic evaluation, melting point, solubility, UV spectroscopy, and FTIR analysis, all of which confirmed the drug's compatibility with the excipients used in the formulation. The drug-loaded nanoemulsions were further evaluated for particle size, polydispersity index (PDI), zeta potential, and scanning electron microscopy (SEM) analysis. The drug-loaded emulgel was characterized for physical appearance, pH, viscosity, spreadability, drug content, in vitro drug release, antifungal activity, and accelerated stability. Results indicated that the Naftifine Hydrochloride - loaded nanoemulgel has potential as an effective delivery system, offering controlled drug release through percutaneous absorption. This formulation also demonstrated enhanced stability, making it a promising candidate for the treatment of fungal infections with prolonged therapeutic effects.

KEYWORDS: Naftifine Hydrochloride, electron microscopy, Zeta potential, Nanoemulsion.

1. INTRODUCTION

Naftifine Hydrochloride is a highly effective antifungal agent commonly used for treating skin infections caused by fungi such as Trichophyton, Microsporum, and Epidermophyton. It is particularly potent in the treatment of Tinea pedis (athlete's foot), a condition that affects about 10% of the global population. Naftifine Hydrochloride is classified as a BCS Class IV drug, meaning it has poor water solubility and low permeability, which limits its effectiveness in topical treatments. To overcome these challenges, developing an emulsion formulation for Naftifine Hydrochloride seems to be a promising solution. Emulsions are known to improve the solubility and absorption of hydrophobic (water-insoluble) drugs.

Topical drug delivery, in general, is preferred in many cases because it allows for controlled and sustained drug release over time. This method can be conveniently self-administered and eliminates the need for invasive injections or oral medication, which may come with gastrointestinal side effects. Moreover, topical formulations reduce the risk of adverse effects commonly seen with oral drugs, such as stomach irritation or ulcers. Because of these advantages, topical treatments are particularly useful for managing skin diseases and other conditions, offering better patient compliance and fewer side effects.

The aim of this study was to develop a Naftifine Hydrochloride nanoemulgel (2 % w/w) for topical application. This formulation is designed to provide controlled, prolonged release of the drug, reducing the need for frequent dosing and improving patient adherence to treatment. The study also aimed to evaluate the antifungal activity of the nanoemulgel against Trichophyton rubrum, a common cause of fungal skin infections.

MATERIALS AND METHOD

Materials

Naftifine Hydrochloride was received as a gift sample from Zydus Nagpur. Carbopol 934 from Molychem, Mumbai. Almond Oil, Tween 80 and Propylene Glycol from Research -lab Fine Chem Industry, Mumbai. All other solvent and reagent are used was of analytical grade.

2. EXPERIEMENTAL METHOD

2.1 Identification of Drug

2.1.1 By UV Spectroscopy

The UV spectrum of Naftifine Hydrochloride was obtained using UV-Visible Double Beam Spectrophotometer. Accurately weighed 10 mg of the drug was dissolved in sufficient quantity of methanol. Stock solutions (100 µg/ml) of Naftifine Hydrochloride were prepared in methanol. The UV spectrums were recorded in the range 200-400 nm by using UV-Visible double beam spectrophotometer exhibited wavelength of absorbance maxima at 256 nm. λmax of Naftifine Hydrochloride in Methanol has been shown in the following figure 1.

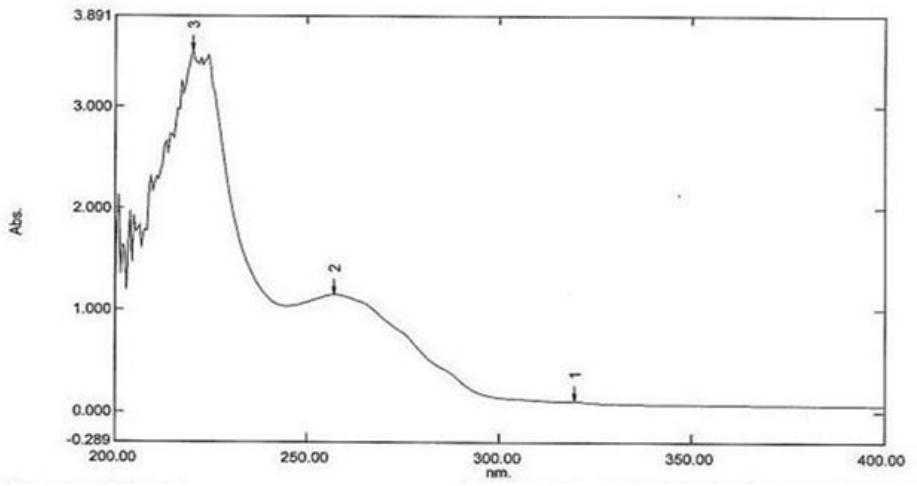

Figure 1: Ultraviolet Spectra of Naftifine Hydrochloride in Methanol.

2.2 Preparation of standard Calibration curve of Naftifine Hydrochloride

Accurately weighed 10 mg Naftifine Hydrochloride and transferred to 10 ml volumetric flask. The volume was made up to 10 ml with methanol and sonicated for 5 min. to produce stock solution of 100 µg/ml. Working standard solutions of strengths 2 -10 µg/ml were made from the stock solution by appropriate dilutions. The above solutions were analysed by UV spectrophotometer at λ max 256 nm. The calibration curve was found to be linear in the concentration range of 100 µg/ml given in following table.

Table 1: Calibration Curve of Naftifine Hydrochloride in Methanol.

Sr. No.	Conc.(ppm)	Absorbance
1	2	0.276
2	4	0.458
3	6	0.680
4	8	0.888
5	10	1.144

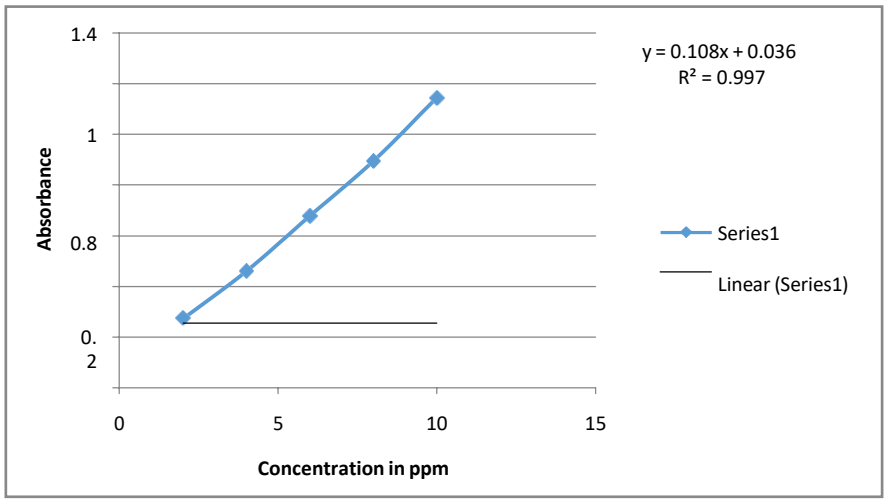

Figure 2: Calibration curve of Naftifine Hydrochloride in Methanol.

2.3 Solubility studies of drug

The solubility of Naftifine Hydrochloride in various oils, surfactants was determined by adding an excess amount of drug to 5 ml of selected oils, surfactants, separately in 10 ml capacity stopper vials, and mixed using a vortex mixer. The mixtures were then kept on magnetic stirrer for 48 hrs at 40±0.5°C (RAJ 305-C). Further kept for 24 hours at room temperature to reach equilibrium. The equilibrated samples were centrifuged at 3000 rpm for 15 min followed by filtration through a 0.45-µm membrane filter. The filtrates were diluted with methanol and Naftifine Hydrochloride solubility was subsequently quantified by UV.

Table 2: Solubility of Naftifine Hydrochloride in different oils.

Sr. No.	Oils	Solubility
1	Castor oil	10.30
2	Oleic acid	12.32
3	Almond oil	31.01
4	Liquid paraffin	9.35
5	Isopropyl myristate	20.67

Table 3: Solubility of Naftifine Hydrochloride in different surfactants and cosurfactant.

Sr. No.	Excipients	Solubility (mg/ml)
1	Tween 20	28.04
2	Span 20	3.06
3	**Tween 80**	**37.29**
4	Span 80	30.43
5	**Propylene glycol**	**35.67**

2.4 Fourier Transform Infrared Spectroscopy

The FTIR spectrum of Naftifine Hydrochloride has been shown in figure 3. The major peaks observed and corresponding functional groups are given in Table 4. The spectrum shows characteristic peaks for Naftifine Hydrochloride.

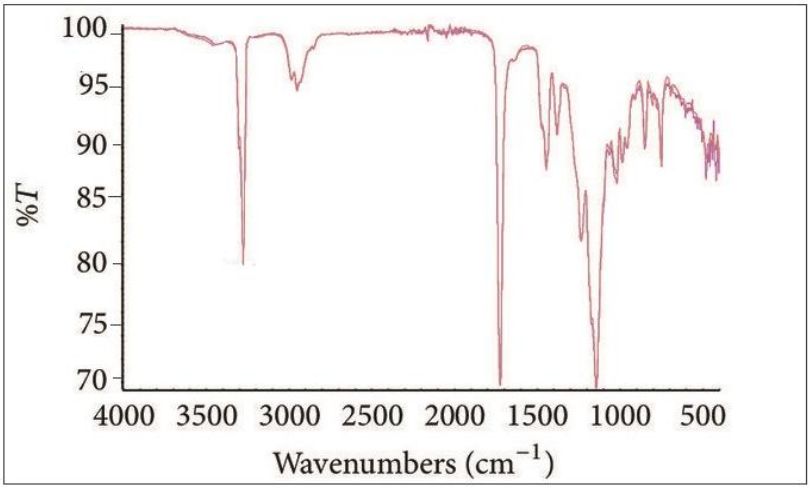

Figure 3: Representative IR spectrum of Naftifine Hydrochlorid.

Table 4: Interpretation of FTIR spectrum of Naftifine Hydrochloride.

Range(cm-1)	Values(cm-1)	Bond
3300-3500	3360	N=H stretching Amines
2800-3000	2906	Aliphatic and Aromatic C-H stretching
1600-1620	1610	Aromatic C=C stretching
1200-1350	1270	C-N stretching
600-800	735	C-Cl stretching

3. Formulation and Development of Nanoemulsion

3.1 3^2 Full Factorial Design

For the present work 3^2 full factorial designs was selected. It has been summarized in Table 5. In this design, 2 factors were evaluated each at 3 levels and experimental trials were performed at all 9 possible combinations as reflected in table no. 6. The two independent variables selected were Almond oil (x1) and Speed of homogenizer (x2).

Table 5: Experimental Design as per 32 Full Factorial Designs.

Formulation code	Coded values		Coded Values	
	X_1	%	X_2	RPM
F1	+1	3	+1	25000
F2	+1	3	0	20000
F3	+1	3	-1	15000
F4	0	2	+1	25000
F5	0	2	0	20000
F6	0	2	-1	15000
F7	-1	1	+1	25000
F8	-1	1	0	20000
F9	-1	1	-1	15000

Table 6: Composition of Nanoemulsion formulation as per 3^2 full factorial designs

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ingredients	%								
Naftifine Hydrochloride (w/w)	2	2	2	2	2	2	2	2	2
Almond Oil (v/v)	3	3	3	2	2	2	1	1	1
Tween 80 (v/v)	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25
Propylene glycol (v/v)	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75
Methyl Paraben (w/w)	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Propyl Paraben (w/w)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
BHT	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Water (v/v)	100	100	100	100	100	100	100	100	100

3.2Method of preparation for Nanoemulsion

The quantities of drug and other ingredients were weighed by calculating equivalent amounts as per table 16 and formulations were prepared in following manner.

Cleaning of glassware and container: All the glassware were washed with distilled water and then sterilized by drying at 160-165^{0}c for 1 hr. in hot airoven.

Preparation of aqueous phase 'A': Accurately weighed quantity of propylene glycol was added into distilled water (80^{0}c).

Preparation of Oil phase 'B': Weighed quantity of Almond oil and tween 80 mixed together by maintaining hot condition, simultaneously accurately weighed quantity of Naftifine Hydrochloride was added into it then addition of methyl paraben, propyl paraben and BHT in it.

Incorporation of solution 'A' in dispersion 'B': Both the phases were mixed properly with the help of High pressure Homogenizer maintaining the respective rpm.

Preparation of gel

Table 6: Composition of gel.

Sr. No.	Ingredients (% w/w)	Quantity
1	Carbopol 934	1%
2	Triethanolamine	0.1%
3	Water (q.s.)	100

3.3 Evaluation of Nanoemulsion

Scanning electron microscopy of Nanoemulsion is shown in figure 4. The shape of Nanoemulsion was Spherical and the size of the Nanoemulsion was below micrometer range. Moreover, the micrograph also revealed the some agglomeration of nanoemulsion which might be due to the evaporation of water present in formulation during sample preparation prior to SEM analysis.

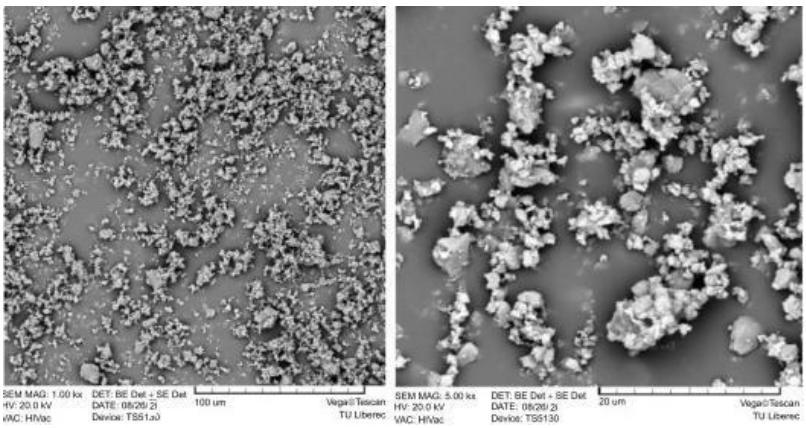

Figure 4: Scanning Electron Microscopy.

3.3.1 Particle Size Analysis

Formulated Nanoemulsion should be analysed for their hydrodynamic particle size. Generally, in case of nanoemulsion dynamic light scattering method used for the measurement of particles and further particle size distribution.

Table 7: Size distribution and PDI.

Formulation code	Particle size (nm)	PDI
Optimized Batch (F1)	100	0.196

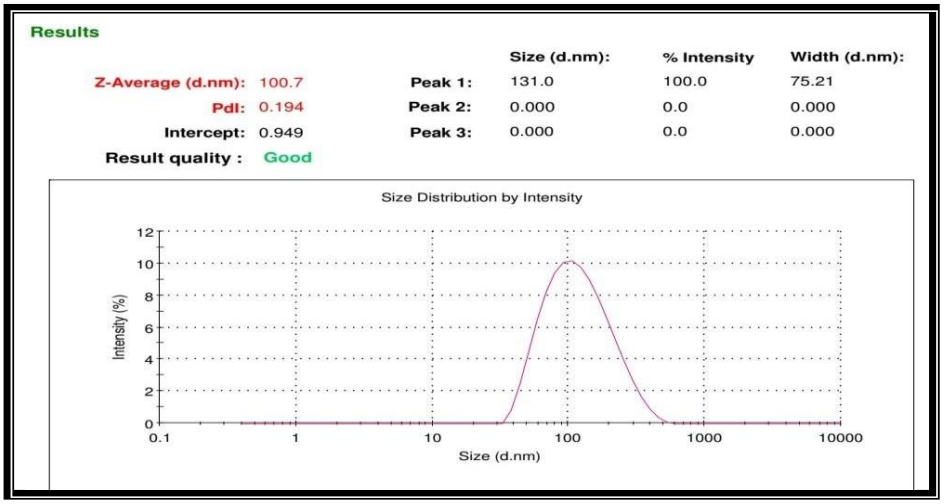

Figure 14: Graph of Particle size of Optimized formulation (F1).

3.3.2 Zeta potential measurements

Zeta potential for nanoemulsion was determined using zetasizerhsa 3000 (Malvern instrument Ltd., UK). Samples were placed in clear disposable zeta cells and results were recorded. Before putting the fresh sample, cuvettes were washed with the methanol and rinsed using the sample to be measured before each experiment.

Table 8: Zeta Potential.

Formulation Code	Zeta Potential
Optimized Batch	-32.0

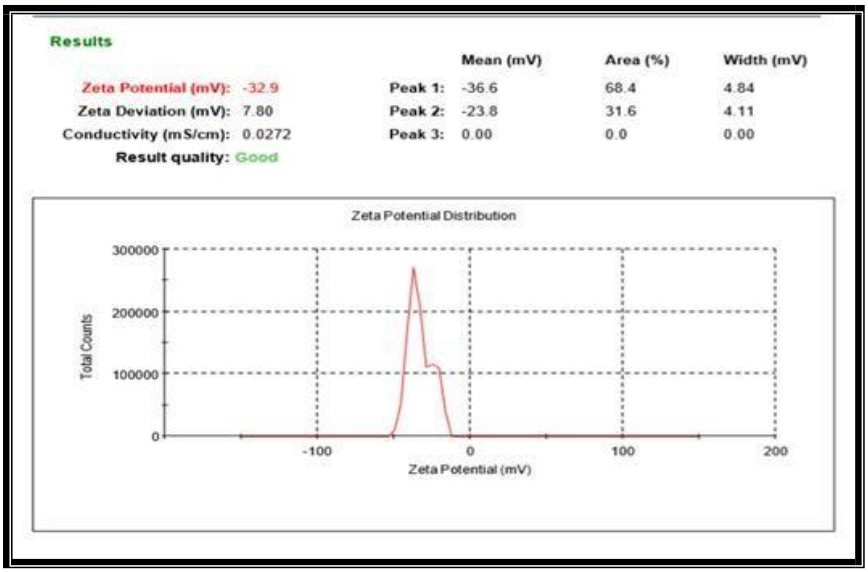

Figure 6: Graph of Zeta Potential of optimized formulation.

4. Evaluation of Emulgel

4.1 Physical appearance

Table 9: Physical appearance of formulations.

Sr. No.	Parameters	Inference
1	Colour	Translucent gel
2	Homogeneity	Homogeneous
3	Consistency	Consistent

4.2 pH

pH of various emulgel are shown in the following table 31 which was found to be in range of 6.31 to 6.84. pH values indicate the suitability of emulgel for topical application, so as to minimize discomfort or irritation due to acidic pH and microbial growth due to basic pH.

Table 10: pH values of formulation.

Sr. No.	Formulation code	Observed pH (± SD)
1	F1	6.61±0.026
2	F2	6.72±0.017
3	F3	6.58±0.012
4	F4	6.46±0.012
5	F5	6.42±0.014
6	F6	6.34±0.010
7	F7	6.30±0.005
8	F8	6.41±0.018
9	F9	6.51±0.027

4.3 Viscosity

The viscosity values of formulations are shown in the following table 11:

Table 11: Viscosity of formulations.

Rpm	Viscosity (cP) at Room Temperature								
	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
10	14960	13450	14500	13750	12500	13500	14500	13500	12000
20	14200	12390	14000	13400	12250	12440	14250	12500	11709
30	13050	12050	13445	12350	11200	12203	13900	12000	10500
40	13000	11500	12230	12010	11000	11253	12750	11500	98500
50	12350	10420	11520	11250	10950	10504	12520	11200	92300

4.4 Spreadability & % Drug Content

Table 12: Spreadability values of formulation.

Sr. No.	Formulation code	Spreadability (g.cm/sec)± S.D.	Drug content (%)± SD
1	F1	17.74 ± 0.025	97±0.5
2	F2	16. 0±0.035	91.81±0.7
3	F3	15.34 ±0.028	96±0.7
4	F4	15.67 ±0.018	93.96±0.7
5	F5	15.10 ±0.032	94. 81±0.7
6	F6	14.82 ± 0.012	73±0.7
7	F7	15.54 ± 0.012	67±1.09
8	F8	15.21 ± 0.011	83±1.07
9	F9	15.86 ±0.018	63.91±1.43

4.5 In-vitro drug release study

The in- vitro release of Naftifine Hydrochloride from its various emulgel formulae are represented in the table 13. It was observed that the release of the drug from optimized (F1) emulgel formulation was higher than the commercial cream. (Tinactin 1 % cream). The drug release of optimized formulation shows the controlled release up to 24 hrs (96 %).

Table 13: Cumulative amount of Naftifine Hydrochloride diffused (%) from all the emulgel formulations through egg membrane using Modified Franz diffusion cell.

Time hrs.	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	9±0.70	8.17±0.76	7.14±0.22	6.25±0.071	6.13±0.75	5.34±0.82	5.01±0.70	3.41±0.85	2.31±0.53
2	17±0.70	14.08±0.73	12.96±0.51	15.22±0.24	11.13±0.75	12.96±1.06	16.74±0.97	19.15±0.75	16.24±0.79
3	25±1.07	24.21±0.74	23.01±0.16	22.11±0.17	23.12±0.74	19.66±0.39	21.30±0.81	18.12±0.74	20.11±0.74
4	34±1.06	32.65±0.38	31.09±0.12	28.23±0.79	26.61±0.84	25.66±0.64	23.49±0.88	22.44±0.31	20.66±0.94
5	41±0.70	40.42±0.85	40.97±0.52	35.49±0.88	30.99±0.50	32.67±0.95	34.69±095	39.45±0.69	39.41±0.85
6	50±0.53	48.57±0.38	47.87±0.47	45.66±0.72	45.35±0.83	40.19±0.19	38.09±0.75	35.66±0.94	30.11±0.74
7	59±1.06	57.45±0.31	55.13±0.94	52.79±0.99	48.49±0.88	44.09±0.10	41.49±0.88	38.09±0.73	37.71±0.96
8	68±1.07	65.15±0.27	62.14±0.16	60.49±0.32	57.18±0.76	54.66±1.2	51.78±0.66	48.83±1	49.89±1.03
12	78±1.41	72.30±0.28	74.25±0.32	64.49±0.33	62.16±0.75	58.19±0.19	56.99±1.07	54.97±1.04	52.31±0.81
16	85±1.04	81.89±0.50	73.41±0.64	70.89±1.05	68.12±0.74	64.69±0.45	61.44±0.86	58.10±0.73	54.14±0.54
24	96±0.66	90±0.38	87.42±0.30	78.94±0.50	72.09±0.73	69.99±1.0	65.05±0.72	61.19±0.76	58.45±1.21

Table 14: Cumulative drug release of formulation F1 and Marketed formulation.

Time (hours)	% Cumulative drug Release + S.D. (F1 formulation)	Time (hours)	% Cumulative Drug Release + S.D. (Marketed formulation)
0	0	0	0
1	9±0.70	1	8±0.77
2	17±0.70	2	15±0.707
3	25±1.07	3	24±0.70
4	34±1.06	4	34±0.70
5	41±0.07	5	42±0.72
6	50±0.77	6	55.57±0.91
7	59±0.70	7	60.45±0.83
8	68±0.71	8	69±0.707
12	78±0.70	9	76.90±705
16	85±0.77	10	82±0.73
24	96±0.71	12	92±0.76

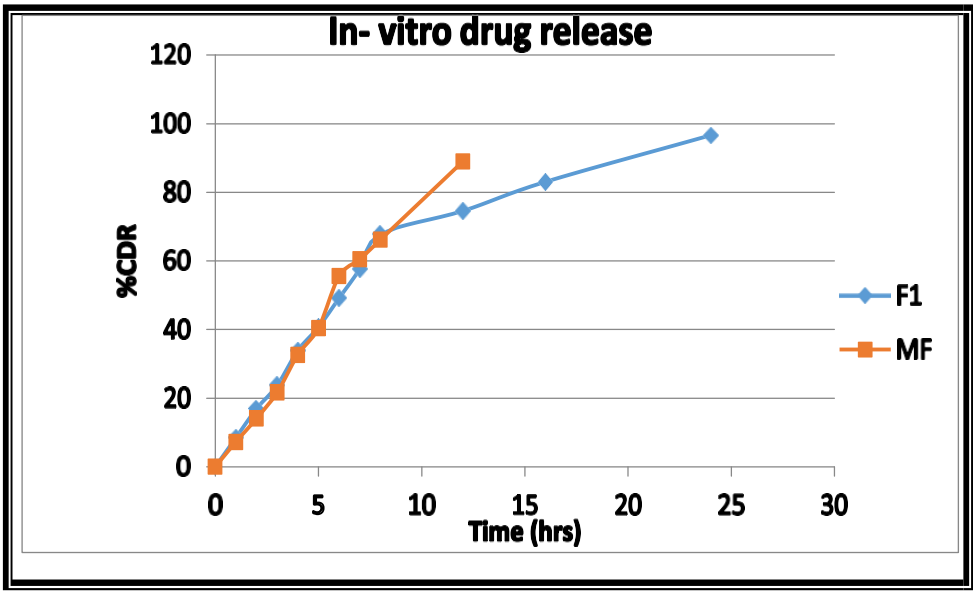

Figure 7: In-Vitro Drug release profile of optimized formulation (F1) and Marketed formulation.

4.5 Accelerated stability studies of Emulgel

Stability studies are performed by guidelines. The organized emulgels were full in aluminum collapsible tubes (5 g) and subjected to strength learns at 5°C, 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH and 60 ± 2° for a period of 3 months. Tests were pulled back at 15 -day time between times and surveyed for physical appearance, pH, rheological properties and pharmaceutical substance.

The optimized formulation was evaluated after storage accelerated condition and Room Temperature. The results of stability studies show that the formulation was stable at Accelerated temperature conditions (400 C± 20 C, 75 % RH ± 5% RH). Results have been given in table 15.

Stability study of Optimized batch F1 was done at Room Temperature.

Table 15: Stability Study data for F1 formulation at Accelerated condition (40^0 C± 2^0 C, 75 % RH±5% RH).

Sr. No	Observations		Before Stability Testing	During study 3rd month
1	Clearity		Translucent	Translucent
2	pH		6.84±0.006	6.80±0.008
3	% Drug content		96±0.5	95.97± 0.5
4	Viscosity	10	12961cp	10233 cp
		20	11590cp	10123cp
		30	11821cp	9876cp
		40	10478cp	10122cp

CONCLUSION

To fulfill all this parameters, drug loaded Nanoemulgel formulations were prepared. Nanoemulsion were prepared by high speed homogenization and studied for different parameters. The problems associated with emulsion stability was also overcome by formulating drug loaded Nanoemulgel by 3^2 full factorial design in which Almond oil (%) and speed of homogenizer (rpm) were taken as independent factors in 3 different levels. Before formulating this formulations Preformulation testing were performed for drug characterization and to analyse its purity and compatibility. Organoleptic properties, melting point, solubility testing, UV spectroscopy studies and FTIR were performed for the Naftifine Hydrochloride and the drug sample procured were found to be and compatible with the excipients used in formulation. For optimization design expert software (version 11) was used. The drug loaded Nanoemulsion's were evaluated for Particle size, Polydispersibility index, Zeta potential and scanning electron microscopy analysis. Drug loaded emulgel were evaluated for physical appearance, pH, viscosity, spredability, drug content, in vitro drug release study(diffusion study), antifungal activity and Accelerated stability studies. The dependent variables Antifungal activity and Diffusion study were statistically evaluated using ANOVA and the 3-D response surfaces were plotted for interpretation.

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