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FORMULATION DEVELOPMENT AND EVALUATION OF TOPICAL NANOEMULGEL OF EBERCONAZOLE NITRATE

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Abstract-

Topical drug delivery can be defined as the application of a drug-containing formulation to the skin for the direct treatment of skin disorders or skin manifestations of systemic disease. For example, psoriasis to limit the pharmacological or other pathological effects of the drug on the skin surface or on the skin. The topical drug delivery system includes a variety of pharmaceutical dosage forms such as semi-solids, liquid preparations, sprays, and solid powders. The most widely used semi-solid preparations for topical drug delivery include gels, creams, and ointments. Antifungal therapy is one of the most effective mechanisms for eliminating fungal infections to improve quality of life. Systemic treatment is usually reserved for nail infections, extensive skin infections, or those that do not respond to topical treatment. Conventional topical formulations cannot maintain and control long-term drug delivery and therefore require longer treatment periods or must be supplemented with oral therapy. Fungal infections require regular application of conventional formulations for a longer period of time. Emulgel will facilitate long-term drug contact with the skin, and also has the ability to change the skin properties of the drug, thus improving the local treatment of skin infections. The strategy is to create a drug contained in Nanoemulgel that can control the release of the drug to the surface of the skin for 24 hours. Emulsion stability problems were also overcome by making a drug-containing Nanoemulgel, where almond oil (%) and homogenization rate (rpm) were considered as toxic factors. create. on 3 different levels.

Keywords- **Topical Preparation, Eberconazole Nitrate, Nanoemulgel, Ringworm.**

I. INTRODUCTION-

Topical drug delivery is a machine that delivers topical medication to any area of the pelvis through ophthalmic, rectal, vaginal, and skin routes as a topical route. The skin is one of the most convenient organs in the human body for topical use and forms the backbone of the local drug delivery apparatus. Topical use can be described as the application of a medicinal ingredient to the skin for the direct

treatment of skin disorders (e.g., acne) or cutaneous manifestations of systemic disease. For example, psoriasis to limit the effects of drugs or diseases deep inside or inside the skin [1].

The topical drug delivery system includes a variety of pharmaceutical dosage forms such as semi-solids, liquid preparations, sprays and solid powders. The most widely used semi-solid preparations for topical drug delivery include gels, creams, and ointments. Most preparations are applied to the skin. Therefore, basic knowledge of the skin and its physiological function is crucial for designing topical dosage forms. The skin of an average adult body covers an area of about 2 square meters and receives about one-third of the blood circulating in the body [2].

It is known that an average human skin surface contains between 40 and 70 hair follicles and 200 to 300 sweat ducts per square centimeter of skin. The pH of the skin varies from 4 to 5.6. Topical nanoemulsions Emulsions are a promising alternative to increase the penetration of drug delivery systems and target poorly soluble drugs, by increasing transdermal absorption, improving retention time in the target region and, ultimately, a reduction in adverse events. The benefits of nanoemulsions with emulsion nanoparticles are independent of the physical properties of the emulsion itself; Importantly, the nanoemulsion also improves the drug's ability to penetrate the skin. Ringworm, also known as ringworm, is a fungal infection of the skin. Typically, this results in a red, itchy, scaly, and circular rash. Hair loss may occur in the affected area. Symptoms begin four to fourteen days after exposure. Several areas may be affected at the same time. About 40 types of fungi can cause ringworm [3].

They are usually of the Trichophyton, Microsporum, or Epidermophyton type. Risk factors include the use of public showers, tactile sports activities such as wrestling, excessive sweating, animal advertising, obesity, and negative immune function. Ringworm can be transmitted by different animals or between people. Diagnosis is usually based solely on appearance and symptoms. It can be shown traditionally or by examining skin pores and scratches under a microscope [4].

Prevention includes keeping skin dry, not going barefoot in public, and sharing private items. Treatment usually includes antifungal creams including clotrimazole or miconazole. If applied to the scalp, oral antifungal medications including fluconazole may be needed. Globally, up to 20% of the population may have ringworm at any given time. Infections in the groin are more common in men, while the scalp and body [5].

II. MATERIALS-

Table no 1. - The Material used in the formulation

Material used	Manufacturer/ Supplier
Eberconazole	Invochem Laboratory.
Almond Oil	Research -lab Fine Chem Industry, Mumbai.
Tween 80	Research -lab Fine Chem Industry, Mumbai.
Propylene Glycol	Research -lab Fine Chem Industry, Mumbai.
Carbopol 934	Molychem, Mumbai
Methanol, Ethanol (Absolute)	Research -lab Fine Chem Industry, Mumbai.
Potato dextrose Agar	Himedia Lab Pvt. Ltd., Mumbai
Triethanolamine (TEA)	Research -Lab Fine Chem Industry, Mumbai.
Potassium dihydrogen phosphate	Research -Lab Fine Chem Industry, Mumbai.
Potassium Phosphate (monobasic)	Research -Lab Fine Chem Industry, Mumbai.

III. PREFORMULATION STUDY-

3.1. Organoleptic Properties-

The drug sample of Eberconazole was evaluated for its organoleptic properties such as appearance, color, odour [6].

3.2. Melting Point:

The melting point of the drug was determined by using open capillary method using the melting point apparatus. The melting point done in triplicate [7].

3.3. Solubility Determination of Eberconazole-

The solubility of Eberconazole 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 Eberconazole solubility was subsequently quantified by UV [8].

3.4. Determination of Maximum absorbance (λ max)-

UV spectrum of Eberconazole obtained using Shimadzu UV. Accurately weighed 10 mg of the drug dissolved in a sufficient amount of methanol. Stock solution (100 µg/ml) of eberconazole was prepared in methanol. UV spectra were recorded in the 200-400 nm range using a UV-Vis dual beam spectrometer. The maximum absorption wavelength (λ max) was determined [9].

3.5. Standard Calibration Curve of Eberconazole in Methanol

Weigh exactly 10 mg of eberconazole and transfer it to a 10 ml volumetric flask. The volume was made up to 10 mL with methanol and soaked for 5 min. to make a stock solution of 100 µg/ml. Working standard solutions of 5-25 ug/ml concentration were prepared from stock solutions using appropriate dilutions. The above solutions were analyzed by UV spectrophotometer at the maximum wavelength of 261 nm [10].

3.6. FTIR spectroscopy-

IR spectra of eberconazole were recorded at wave number 4000 at 50 cm-1 using a Fourier transform infrared spectrometer (Mode-FTIR, Bruker). The method used for analysis is ATR. The above methods measure infrared spectroscopy for powder samples mixed in media such as KBr or liquid paraffin. However, the ATR method is capable of measuring powder samples directly. The attenuated total reflectance (ATR) method involves pressing the sample against a high-index prism and measuring the infrared spectrum using infrared light that is totally reflected inside the prism [11].

Drug excipients compatibility study-

Drug excipients compatibility was performed by liquid FTIR. It was performed by mixing drug with excipients like oil, surfactant and polymer in equal proportion and then IR spectrum was noted for mixture using NaCl cell. Small amount of the mixture was placed on the sample cell, the cell was then fitted in sample holder, spectra were recorded with FTIR instrument and the spectral analysis was done [12].

IV. FORMULATION AND DEVELOPMENT OF NANOEMULSION-

Table no 02 - Composition of Nanoemulsion formulation

Ingredients (%)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Eberconazole (w/w)	10	10	10	10	10	10	10	10	10
Almond Oil (v/v)	3	3	3	2	2	2	1	1	1
Tween 80 (v/v)	5.25	4.50	3.75	5.25	4.50	3.75	5.25	4.50	3.75
Propylene glycol (v/v)	1.75	1.50	1.25	1.75	1.50	1.25	1.75	1.50	1.25
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

4.2. Method of preparation for Nanoemulsion-

The amounts of the drug and other ingredients were balanced by calculating the equivalent amounts according to Table 16 and the formulations were prepared as follows. Cleaning of glassware and containers All glassware was washed with distilled water and then sterilized by drying at 160-1650°C for 1 h. in a hot air oven. To prepare for the first stage, a precisely weighed amount of propylene glycol was added to distilled water (800°C). while for the preparation of phase 2, a weighed amount of almond oil and tween almond oil are mixed together to maintain warm conditions, a precisely weighed amount of eberconazole is added to it, and methylparaben is added. propyl paraben and BHT. The two phases are then mixed evenly using a high-pressure homogenizer that maintains the respective machine rpm [13,14].

4.3. Preparation of gel-

Table no 03 - Composition of gel

Ingredients (% w/w)	Quantity
Carbopol 934	1%
Triethanolamine	0.1%
Water (q.s.)	100

Weighed amounts of carbopol 934 were mixed in distilled water (400 °C), with the addition of triethanolamine to maintain the desired pH range of the solution. The homogeneity of stirring was maintained after which the gel was stored in the refrigerator for 24 h [15].

4.5. Preparation of Emulgel:

Further incorporation of 10% nanoemulsion containing 10% drug was incorporated to obtain 100 % (w/w) emulgel.

4.6. Filling to container-

The formulation was transferred into previously cleaned and dry containers.

V. EVALUATION OF NANOEMULSION-

5.1. Appearance-

The prepared nanoemulgel formulations were inspected visually for their colour, homogeneity, consistency and pH. The pH values of 0.1% aqueous solutions of the prepared Gellified Emulsion were measured by a pH meter [16,17].

Scanning Electron Microscopy-

The morphology of nanoemulsion can be determined by scanning electron microscopy (SEM). SEM gives a three-dimensional image of the partical. The samples are examined at suitable accelerating voltage, usually 20 kV, at different magnifications. A good analysis of surface morphology of disperse phase in the formulation is obtained through SEM. Image analysis software, may be employed to obtain an automatic analysis result of the shape and surface morphology [18].

5.2. 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 [19].

5.3. Zeta potential measurements-

Zeta potential for nanoemulsion was determined using zetasizer hsa 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 [20].

5.4. Entrapment efficiency-

Entrapment efficiency is defined as the percentage amount of drug which is entrapped by the Nanoemulsion. For the determination of entrapment efficiency, the unentrappped drug was first separated by centrifugation at 15000 rpm for 30 minutes. The resulting solution was then separated and supernatants liquid was collected. The collected supernatants were then diluted appropriately with methanol and estimated using UV visible spectrophotometer at 261 nm [21].

VI. EVALUATION OF NANOEMULSION BASED GEL-

6.1. Determination of pH-

pH of the formulation was determined by using digital pH meter. pH meter electrode was washed by distilled water and then dipped into formulation to measure pH and this process was repeated 3 times [22].

6.2. Measurement of viscosity-

The viscosity of the formulated batches was determined using a Brookfield Viscometer (RVDV-I Prime, Brookfield Engineering Laboratories, USA) with spindle 63. The formulation whose viscosity was to be determined was added to the beaker and was allowed to settle down for 30 min at the assay temperature (25±1ºC) before the measurement was taken. Spindle was lowered perpendicular in to the centre of emulgel taking care that spindle does not touch bottom of the jar and rotated at a speed of 50 rpm for 10 min. The viscosity reading was noted [23].

6.3. Spreadability-

To determine spreadability of the gel formulations, two glass slides of standard dimensions were selected. Formulation whose spreadability was to be determined was placed over one slide and the other slide was placed over its top such that the gel is sandwiched between the two slides. The slides were pressed upon each other so as to displace any air present and the adhering gel was wiped off. The two slides were placed onto a stand such that only the lower slide is held firm by the opposite fangs of the clamp allowing the upper slide to slip off freely by the force of weight tied to it. 20 gm weight was tied to the upper slide carefully. The time taken by the upper slide to completely detach from the lower slide was noted. The spreadability was calculated by using the following formula [24-26].

$$S = M. L/T$$

Where, M = weight tied to upper slide

L = length of glass slides

T = time taken to separate the slides

6.4. Drug content study-

Drug content study was done to determine the amount of the drug present in the certain quantity of the formulation. Took 1 g of the formulation into 10 ml volumetric flask added methanol in it and shake well and make up the volume with methanol. The Volumetric flask was kept for 2 hr and shaken well in a shaker to mix it properly. The solution was passed through the filter paper and filtered the mixer then measured absorbance by using spectrophotometer at 261 nm [27-30].

6.5. In-vitro Drug release study-

The in vitro drug release studies of the Emulgel were carried out on Diffusion cell using egg membrane. This was clamped carefully to one end of the hollow glass tube of dialysis cell. Emulgel (1gm) was applied on to the surface of egg membrane dialysis membrane. The receptor chamber was filled with freshly prepared PBS (pH 7.4) solution. Total amount of gel filled in the tube to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1ml aliquots) were collected at suitable time interval sample were analyzed for drug content by UV visible spectrophotometer at 261 nm after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval. The cumulative amount of drug release across the egg membrane was determined as a function of time. The cumulative % drug release was calculated using standard calibration curve [31,32].

Table no 04 - Parameters in Diffusion study

Parameters	
Reference apparatus for test:	Franz Diffusion Cell
Mode of Agitation	Magnetic Stirrer (50 rpm)
Mode of Temperature control	Thermostat (37± 0.5^{0}C)
Donor Compartment	One side open ended tube, 24 mm diameter
Receptor Compartment	250 ml, beaker containing 100 ml phosphate buffer solution pH 7.4
Semi-permeable membrane	Egg membrane

6.6. Release kinetics of selected formulation-

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing Zero order (cumulative % drug release v/s. time), First order (log cumulative % drug retained v/s. time), Higuchi model (cumulative % drug retained v/s. Square root of time) [33].

6.7. Optimization Study-

All experiments were performed in triplicates. All data are reported as mean ± standard deviation (SD) and the groups were compared using ANOVA, with $p<0.05$ considered statistically significant [34].

6.8. 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 [35].

VII. RESULT AND DISCUSSION

7.1. Preformulation study-

7.1.1. Organoleptic properties-

Eberconazole was studied for its organoleptic properties such as appearance, colour and odour. The result shows the details of organoleptic properties of Eberconazole were found to be similar as mentioned in literature.

Table no 05 - Organoleptic properties of Eberconazole

Drug	Properties	Observed Results
Eberconazole	Appearance	Crystalline powder
	Colour	White
	Odour	Slight Odour

7.1.2. Melting Point-

The melting point of compound was measured and reported as follows.

Table no 06 - Melting Point of Eberconazole

Drug	Observed Value	Reported Value
Eberconazole	170^0c	170-172^0c

All the physical properties of the drugs were within the limit of reported standards which assures the purity of the drug samples.

7.1.3. Solubility

Solubility of Eberconazole has been tabulated in the following table:

Table no 07 - Solubility of Eberconazole

Solvent	Solubility
Water	Slightly soluble
Acetonitrile	Soluble
0.1 N HCl	Soluble
Phosphate Buffer 6.8	soluble

Solubility and its solubility features was utilised for the UV spectroscopy and drug content.

7.1.4. Determination of (λ_{max}) of Eberconazole in Methanol-

The UV spectrum of Eberconazole solution (100µg/ml) scanned between 400-200 nm using UV spectrophotometer exhibited wavelength of absorbance maxima at 261 nm. λmax of Eberconazole in Methanol has been shown in the following figure 13.

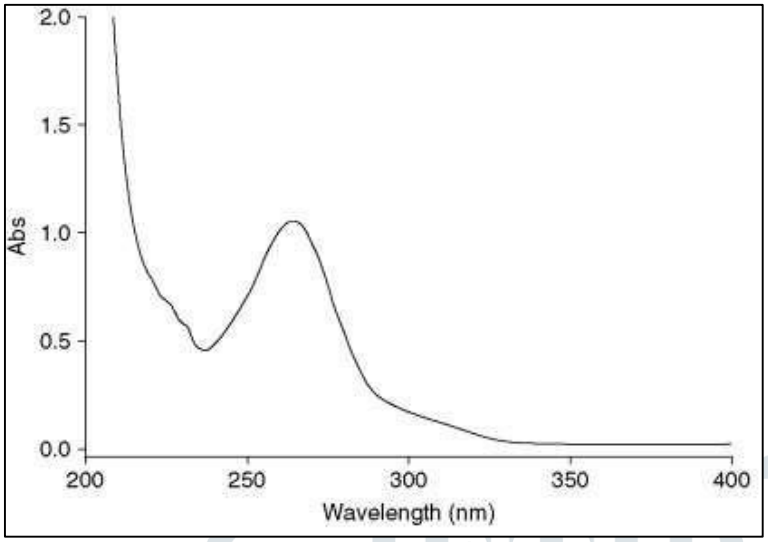

Figure no 01- Ultraviolet Spectra of Eberconazole in Methanol

7.1.5. Calibration of Eberconazole in Methanol-

Calibration curve of Eberconazole was performed in methanol as Eberconazole is soluble in methanol. Methanol solution of drug was very clear and readily analysed by the UV- visible spectrophotometer. The calibration curve was found to be linear in the concentration range of 100 µg/ml given in following table.

Table no 08 - Calibration Curve of Eberconazole in Methanol

Conc.(ppm)	Absorbance
5	0.2136
10	0.4159
15	0.5894
20	0.7689
25	0.9736

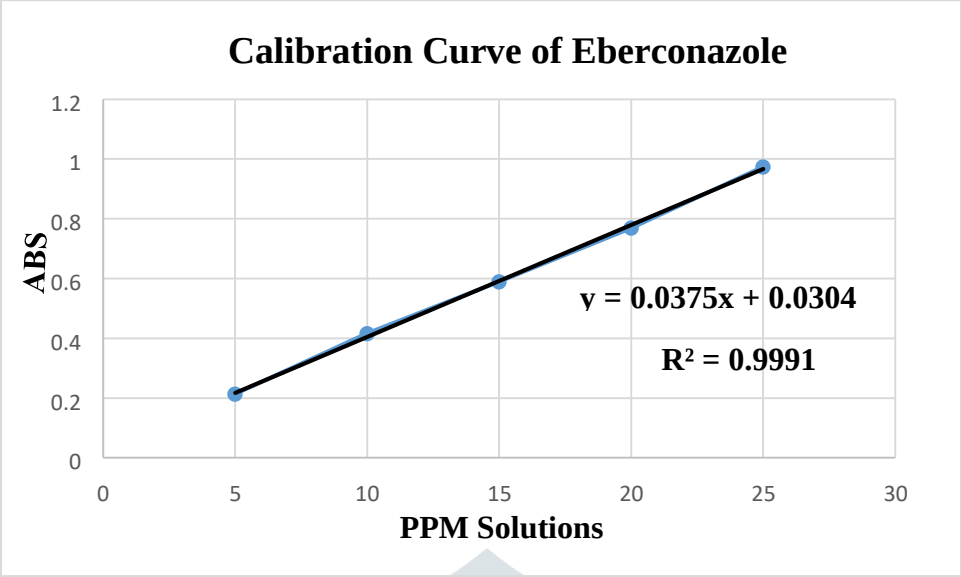

Figure no 02 - Calibration curve of Eberconazole in Methanol

7.1.6. Solubility determination of Eberconazole-

Solubility study of drug in different oils-

Table no 09 - Solubility of Eberconazole in different oils

Oils	Solubility
Castor oil	9.61
Oleic acid	10.5
Almond oil	25.67
Liquid paraffin	8.94
Isopropyl myristate	21.06

Solubility of Eberconazole in different oils was determined and indicated in above table.

Solubility determination of Eberconazole in surfactants and co-surfactant

Table no 10 - Solubility of Eberconazole in different surfactants and co-surfactant

Excipients	Solubility (mg/ml)
Tween 20	27.15
Span 20	4.56
Tween 80	35.64
Span 80	29.16
Propylene glycol	36.05

7.1.7. Fourier Transform Infrared Spectroscopy-

The FTIR spectrum of Eberconazole has been shown in figure 15. The major peaks observed and corresponding functional groups are given in Table 22. The spectrum shows characteristic peaks for Eberconazole.

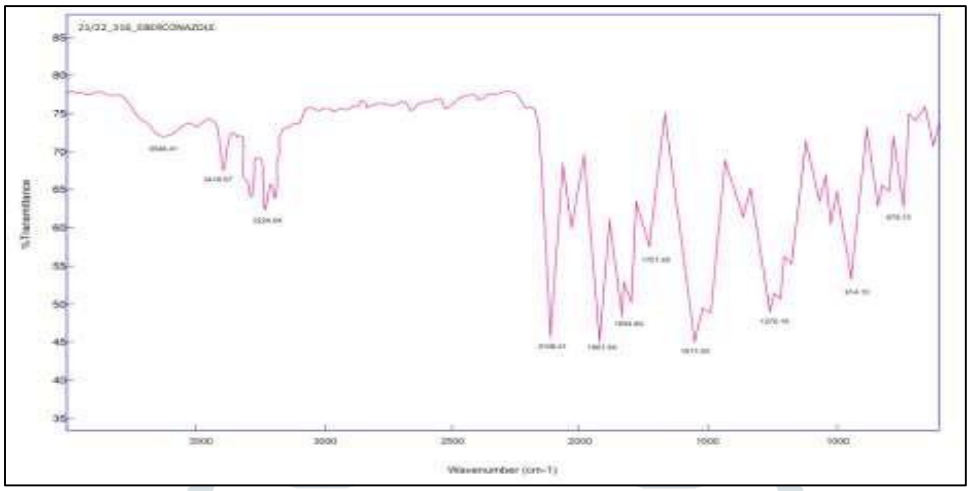

Figure no 03 - Representative IR spectrum of Eberconazole

Table no 11 - Functional groups present in I.R. of Eberconazole

Functional Group	Observation (cm^{-1})	Standard (cm^{-1})
NH Stretch	3418.57	3500-3100
C-H Stretch	3224.64	3300-3000
C=H	2106.41	2200-2050
C=C	1901.64	2100-1800
C-CI	914.15	1050-650

The absorption bands shown by Eberconazole are characteristics of the groups present in its molecular structure. The presence of absorption bands corresponding to the functional groups present in the structure of Eberconazole confirms the identification and purity of the Eberconazole sample used in the study.

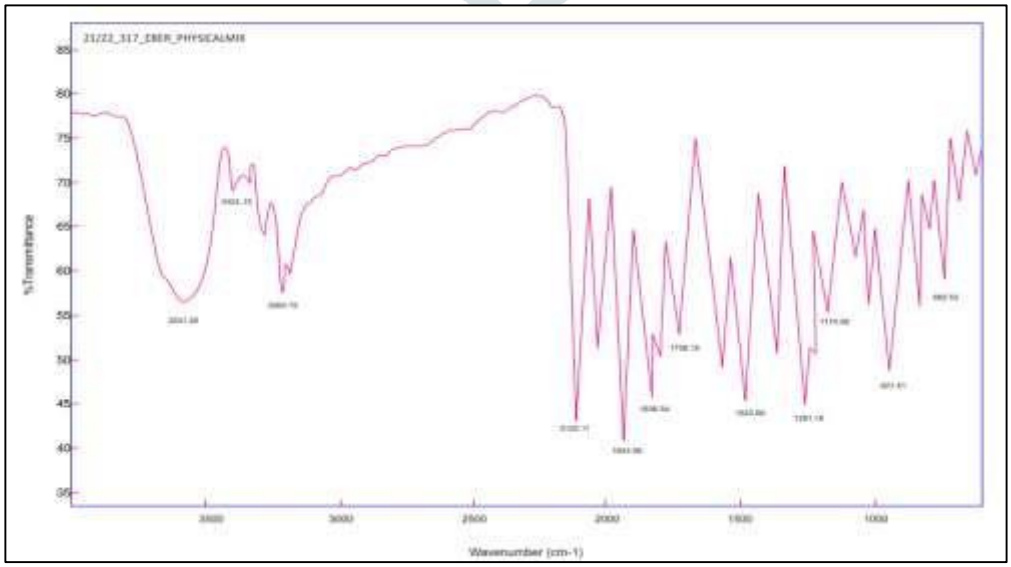

Fig no 04 - FTIR of Physical mixture

Table no 12 - Interpretation of FTIR Spectrum of physical mixture

Functional Group	Peaks	
	Pure Drug	Physical Mixture
NH Stretch	**Yes**	**Yes**
C-H Stretch	**Yes**	**Yes**
C=N	**Yes**	**Yes**
C=C	**Yes**	**Yes**
C-Cl	**Yes**	**Yes**

7.2. Formulation, Development and evaluation of Topical nanoemulgel of Eberconazole-

The various formulation prepared have been shown in following figure.

Figure no 05 - Formulation of F1 to F9 batch

7.2.1. Entrapment Efficiency-

The maximum Entrapment efficiency was found to be 96.1% and the minimum Entrapment efficiency was found to be 70.6% in figure. It has been observed that the drug entrapment efficiency was highest for optimized batch (F1).

Table no 13 - Entrapment efficiency of formulation F1 to F9.

Formulation code	% Entrapment Efficiency
F1	96.1
F2	95.6
F3	90.1
F4	88.4
F5	85.4
F6	71.0
F7	75.1
F8	70.6
F9	85

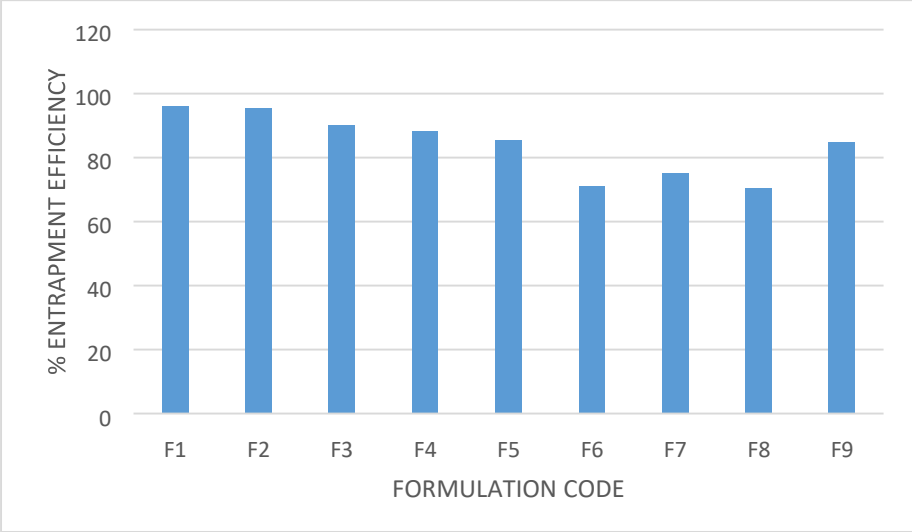

Figure no 06 - Entrapment efficiency of F1 to F9

7.2.2. Particle size and poly dispersibility index-

The Particle size of the Nanoemulsion of optimised batch was found to be 100 nm. It is seen with increase in concentration of Almond oil with high speed of homogenizer decrease in particle size.

Table no 14 - Size distribution and PDI

Formulation code	Particle size (nm)	PDI
Optimized Batch (F1)	131	0.184

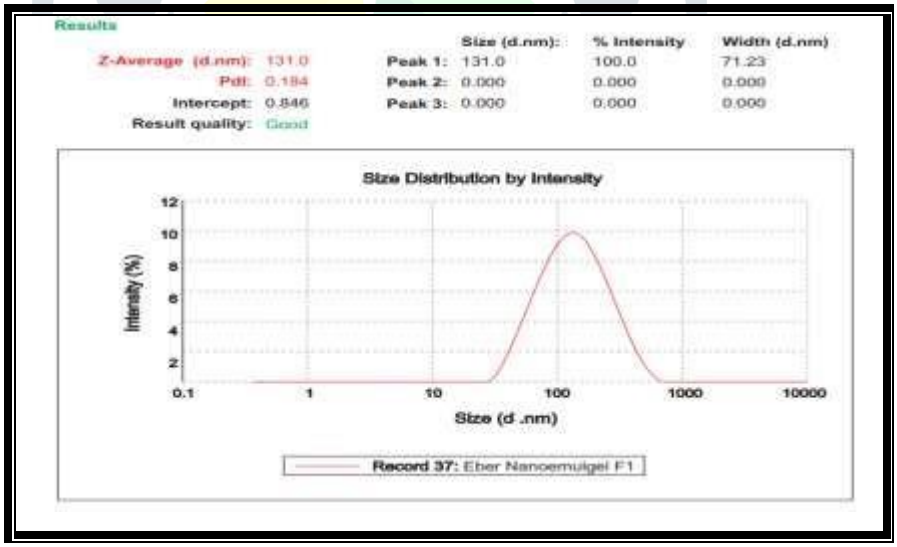

Figure no 07 - Graph of Particle size of Optimized formulation (F1)

7.2.3. Zeta Potential-

Zeta potential shows the stability of the (colloidal dispersion) nanoemulsion under the stress testing condition according to ICH guidelines of stability studies of various pharmaceutical formulations. Zeta potential is affected by particle size, lowest particle size in nano size i.e. 100, shows -29.5 mV. Zeta potential which indicate thermodynamic instability of the dispersion.

Table no 15 - Zeta Potential

Formulation Code	Zeta Potential
Optimized Batch	-29.5

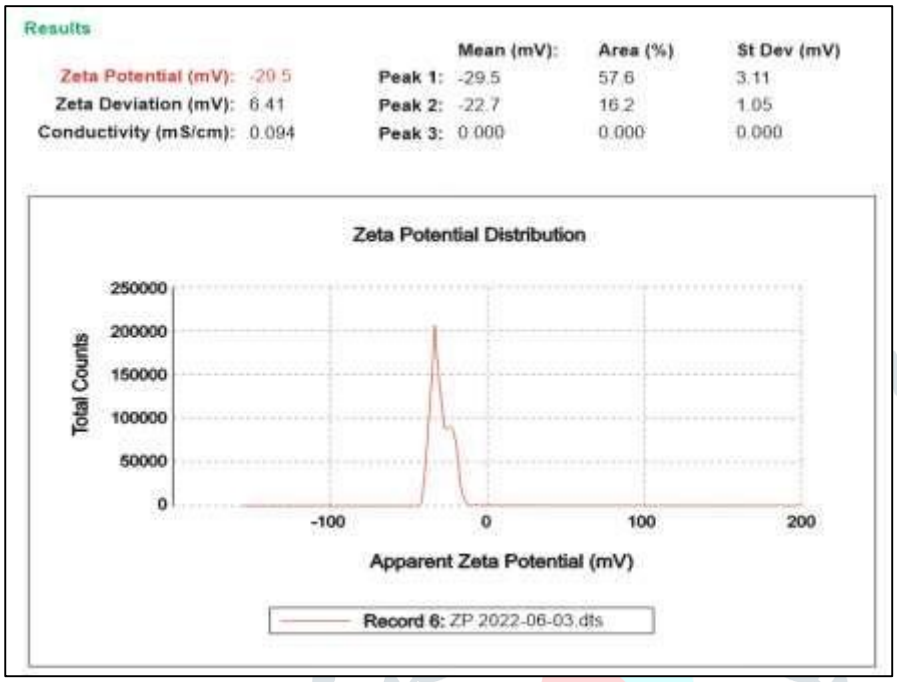

Figure no 08 - Graph of Zeta Potential of optimized formulation

7.2.4. Scanning Electron Microscopy-

Scanning electron microscopy of Nanoemulsion is shown in figure. 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.

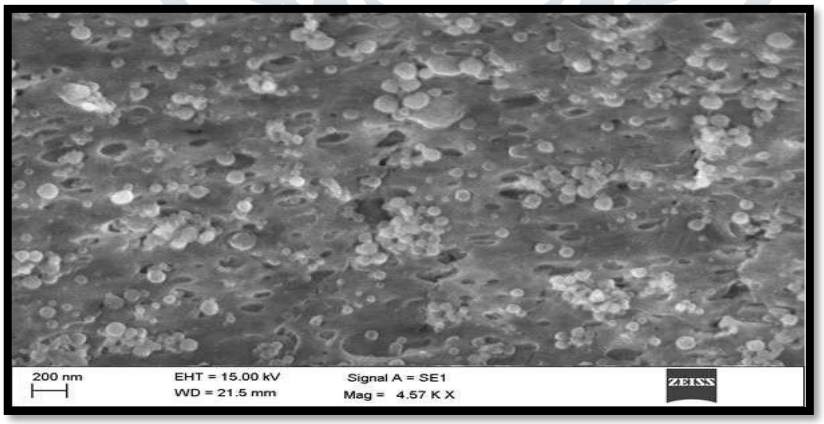

Figure no 09 - Scanning Electron Microscopy

7.3. Evaluation of Emulgel-

7.3.1. Physical appearance-

Table no 16- Physical appearance of formulations

Parameters	Inference
Colour	Translucent gel
Homogeneity	Homogeneous
Consistency	Consistent

The physical appearance of the emulgel formulation was found to be Translucent, homogeneous and consistent.

7.3.2. pH-

pH of various emulgel are shown in the following table 28 which was found to be in range of 5.05 to 5.92 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 no 17- pH values of formulation

Formulation code	Observed pH (± SD)
F1	5.56
F2	5.41
F3	5.92
F4	5.24
F5	5.63
F6	5.14
F7	5.05
F8	5.84
F9	5.47

7.3.3. Viscosity

The viscosity values of formulations are shown in the following table-

Table no 18 - Viscosity of formulations

Rpm	Viscosity (CP) at Room Temperature								
	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
10	14659	14025	14264	14365	13655	13664	13986	13894	13564
20	14102	13648	14102	13787	12664	12054	13264	13024	12548
30	13865	12645	13841	12745	12024	11546	12856	12874	11544
40	12984	11652	12635	11566	11654	11054	12054	11987	10645
50	12325	10254	11424	10325	11265	9634	11856	10953	9841

Emulgel spreadability is important in topical emulgel formulations. Spreadability shows an inverse relationship with emulgel viscosity. Higher viscosity formulations are very dense in nature, difficult to spread; conversely, emulsifiers with too low viscosity are liquid, two extremes unsuitable for any topical formulation. Therefore, gels with optimum viscosity provide appropriate spreadability for formulations. Formula F1, has an optimal viscosity and spreadability of this formulation of 18.14 g.cm/sec

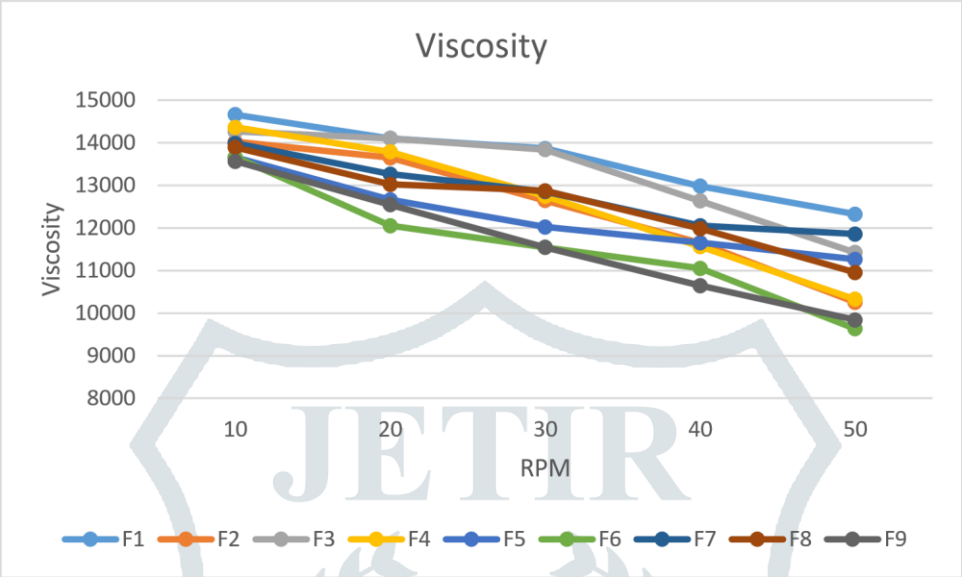

Figure no 10 - Viscosity of formulation

7.3.4. Spreadability-

Emulgel spreadability is important in topical emulgel formulations. Spreadability shows an inverse relationship with emulgel viscosity. Higher viscosity formulations are very dense in nature, difficult to spread; conversely, emulsifiers with too low viscosity are liquid, two extremes unsuitable for any topical formulation. Therefore, gels with optimum viscosity provide appropriate spreadability for formulations. Formula F1, has an optimal viscosity and spreadability of this formulation of 18.14 g.cm/sec.

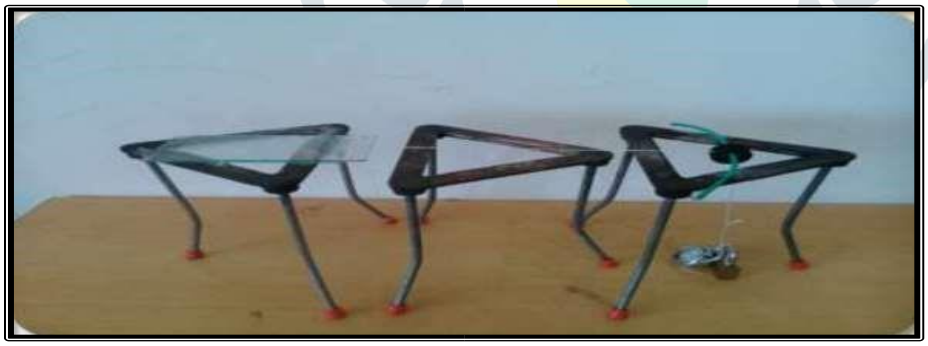

Fig ure 11: Spread ability Apparatus

Table no 19 - Spreadability values of formulation

Formulation code	Spreadability (g.cm/sec)± S.D.
F1	18.14
F2	16.02
F3	15.45
F4	14.26
F5	15.48
F6	14.94
F7	16.55
F8	14.02
F9	13.68

7.3.5. Drug Content

The drug content of formulation has shown in following table.

Table no 20- Drug content of formulation

Formulation code	Drug content (%)± SD
F1	97.15
F2	96.12
F3	95.05
F4	92.48
F5	91.45
F6	94.16
F7	96.15
F8	94.74
F9	93.46

The percentage drug content of all formulated emulgel formulations ranges from 91-97%. Therefore, content uniformity was maintained across all formulations. The drug content of the F1 formulation is 97%.

7.3.6. In-vitro drug release study-

Table no 21 - *in- vitro* release of Eberconazole from its various emulgel formulae are represented in the table

Time hr	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	9.56	8.64	9.65	5.69	4.16	6.56	6.56	5.61	3.15
2	15.26	12.64	15.26	10.59	12.64	15.46	20.16	15.16	23.16
3	25.64	24.6	20.26	25.94	20.49	21.26	20.31	18.16	22.31
4	31.64	32.64	26.46	27.59	25.46	22.94	23.96	22.16	25.46
5	39.64	41.6	31.6	30.19	33.64	35.49	30.23	28.64	35.16
6	46.45	45.4	42.95	43.19	40.49	39.46	39.14	32.46	40.16
7	58.56	55.46	51.06	45.94	45.16	42.64	42.1	36.54	43.61
8	66.6	60.12	59.54	55.40	55.4	52.08	48.46	42.15	50.14

12	75.46	74.6	63.19	61.02	59.16	56.49	55.12	56.94	59.14
16	85.16	76..12	69.94	67.94	65.46	62.12	59.51	60.16	68.41
24	96.16	80.46	72.49	75.06	70.16	66.19	62.01	65.51	76.14

The in- vitro release of Eberconazole from its various emulgel formula are represented in the table.

Table no 22 - Cumulative drug release of formulation F1 and Marketed formulation (Ebernet)

Time (hr)	% Cumulative drug Release + S.D. (F1 formulation)	Time (hours)	% CDR Marketed formulation (Ebernet)
0	0	0	0
1	9.56	1	8.32
2	15.26	2	13.25
3	25.64	3	24.65
4	31.64	4	32.15
5	39.64	5	40.41
6	46.45	6	47.95
7	58.56	7	56.41
8	66.6	8	62.63
12	75.46	9	72.15
16	85.16	10	83.14
24	96.16	12	92.36

It was observed that drug release from an optimized emulgel formulation (F1) was superior to that of a commercial gel. (0.1% gel). The optimized formulation's drug release shows controlled release up to 24 hours (96%) and the commercially available formulation shows (92%) drug release up to 12 hours. Formula F1 showed steady state release for up to 24 h, which also indicates that this formulation would exhibit better exposure to biofilm. The drug is trapped in the oil phase, so once the formulation has been applied to the egg membrane, penetration occurs for up to 24 hours. This drug release phenomenon also suggests that when such formulations are applied to the skin surface, drug diffusion follows the mechanism.

The drug adsorbed on the nano-emulsion diffuses rapidly through the stratum corneum and is readily available in the epidermis. Formulas with a more miniaturization effect will follow this mechanism since the drug is more freely available on the surface. Drugs embedded in nano-emulsions can penetrate the skin surface by diffusion, and this washed-out drug can further diffuse through the stratum corneum. Nanoemulsions with low trapping efficiency also follow this principle in addition to principle A above. It, therefore, indicates rapid drug availability in the epidermal region. The highest drug-loaded nanoemulsion monitors drug diffusion by following the mechanism, i.e. skin moisturizing is enhanced by preventing trans-epidermal water loss due to the gel loaded in the nano-emulsion. Nano-emulsions migrate to the skin with higher water concentration through the stratum corneum due to longer hydration times, nano-emulsions are applied through large pores and nano-emulsions are available in the epidermal area. From the pre-existing epidermal nanoemulsion, the drug is released in a controlled manner, which enhances the antifungal activity of the drug trapped in the nanoemulsion.

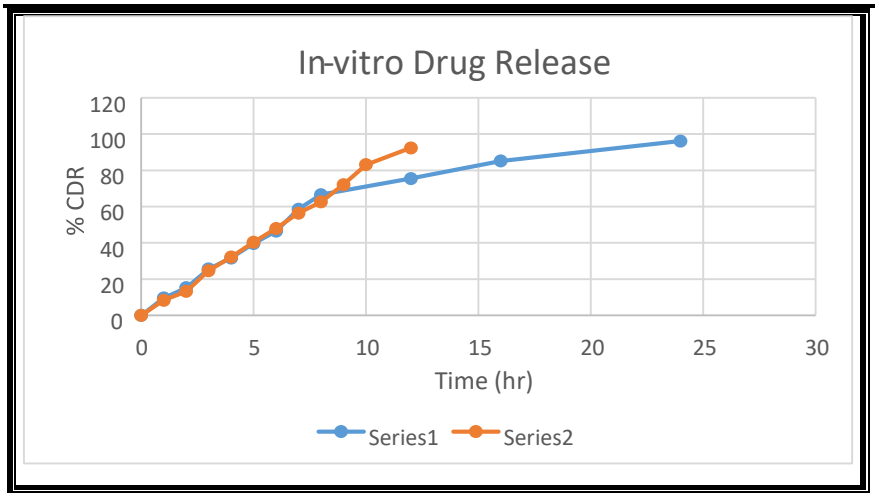

Figure no 12 - *In-Vitro* Drug release profile of optimized formulation (F1) and Marketed formulation.

7.3.7. Drug release Kinetics-

In the present study, the drug release was analysed to study the kinetics of drug release mechanism. The results for zero order model kinetics and Higuchi model kinetics have shown in following.

7.3.8. Comparative evaluation of Zero order kinetic model-

Zero order describes the system where the release rate of drug is independent of its concentration. The equation is:

$$C = CO\text{-}K0\ t$$

Where,

C = Amount of drug release or dissolved

C0 = Initial amount of drug in solution

K0 = Zero order rate constant t = Time for study of release kinetics

The graph plotted between cumulative amounts of drug release v/s time.

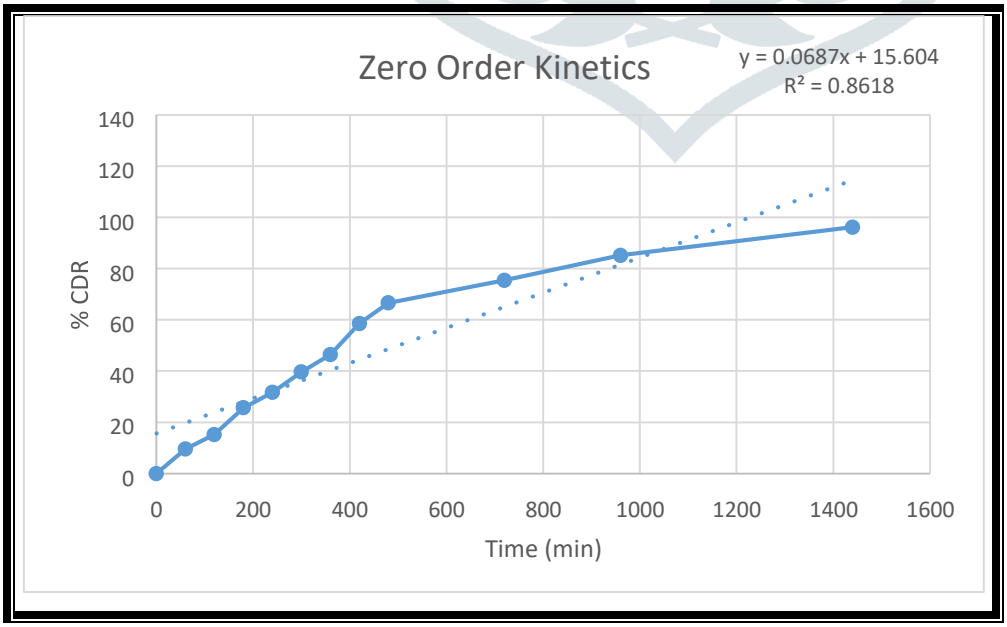

Figure no 13 - Model graph for comparative evaluation of Zero Order Kinetics

Table no 23- R2 Value for the optimized formulation of Zero Order Kinetic

Batch	R2 value	Slope
F1	0.8618	0.0687

7.3.9. Comparative evaluation of Higuchi Kinetic model-

Higuchi developed model to study the release of water soluble and low soluble drugs incorporated in semisolid and solid matrices. To study the dissolution from a planer system having a homogeneous matrix the relation obtained as

$$A = [D (2C - Cs) Cs \times t]^{1/2}$$

Where,

A: Amount of drug release in time‘t’ per unit area

B: Diffusivity of drug molecule in matrix in substance

C: Initial drug concentration

Cs: Drug solubility in matrix area.

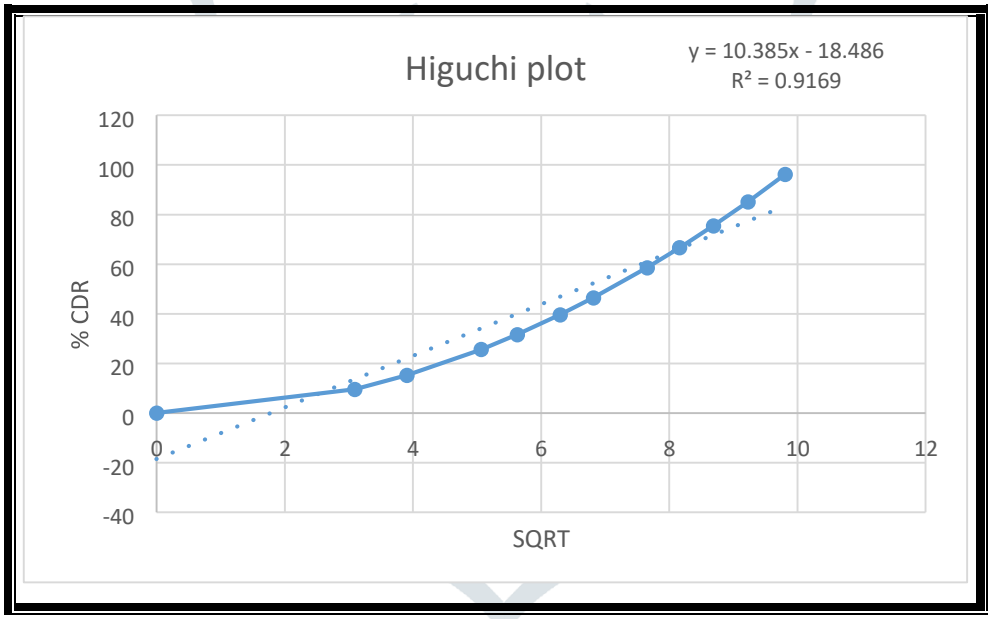

Figure no 14 - Model graph for comparative evaluation of Higuchi Kinetics

Table no 24 - R2 value for formulation F1 for Higuchi Kinetics

Batch	R2 value	Slope
F1	0.9169	10.385

In the zero-order drug release study and Higuchi kinetics study, it was found that the optimized formulation exhibits the Higuchi mechanism based on drug diffusion and nanoemulsion from the frost matrix.

7.4. Evaluation of Optimized batch

7.4.1. Best fit kinetic model for optimized formulation

The most suitable kinematic model for the optimization formula with the highest R2 value and the lowest slope value is the Higuchi model. The R2 value for the Higuchi model of the optimized formulation indicates that drug release occurs by diffusion.

Table no 25 - R2 and slope values for optimized formulation F1

Model	R^2	Slope
Zero-order	0.8618	0.0687
Higuchi	0.9169	10.385

The classical zero-order release curve was found to be linear. The curve plotted for the Higuchi release model was found to be linear. For the curves of the Higuchi release model, R2 was found to be 0.9169, R2 for zero-order release was found to be 0.8618 for the optimized formulations. The most suitable kinematic model for the optimization formula with the highest R2 value and the lowest slope value is the Higuchi model. This indicates that the formulation shows possible drug release by diffusion.

7.4.2. Stability study-

The optimized formulation was evaluated after storage under accelerated conditions and at room temperature. The results of stability studies show that this formulation is stable under accelerated temperature conditions (400 C ± 20 C, 75% RH ± 5% RH). The results are presented in Table. The stability study of the optimized batch F1 was performed at room temperature.

Table no 26 - Stability Study data for F1 formulation at Accelerated condition (400 C± 20 C, 75 % RH±5% RH)

Observations		Before Stability Testing	During study 3rd month
Clarity		Translucent	Translucent
pH		5.56	5.12
% Drug content		96±0.5	95.97± 0.5
Viscosity	**10**	14659	14236
	20	14102	14100
	30	13865	13984
	40	12984	12845
	50	12325	12236

VIII. CONCLUSION-

Antifungal therapy is one of the most effective mechanisms for eliminating fungal infections to improve quality of life. Systemic treatment is usually reserved for nail infections, extensive skin infections, or those that do not respond to topical treatment. For all these parameters, a Nanoemulgel formulation containing the drug has been formulated. Nanoemulsions were prepared by high-speed homogenization and studied various parameters. Emulsion stability problems were also overcome by making a drug-containing Nanoemulgel in which almond oil (%) and homogenization rate (rpm) were taken as independent factors at 3 levels. different degrees. Prior to the formulation of these formulations, pre-preparation tests were performed to characterize the drug and analyze its purity and compatibility. Sensory properties, melting point, solubility testing, UV spectroscopy, and FTIR studies were performed for Eberconazole

and the purchased sample was found to be compatible with the excipients used. in the formula. The drug-loaded nanoemulsion was evaluated for particle size, polychromatic dispersion index, and zeta potential, and analyzed by scanning electron microscopy. Drugs containing emulsions have been evaluated for appearance, pH, viscosity, spreadability, drug content, in vitro drug release studies (diffusion studies), stability and resolution studies. drug release 'accelerator. antifungal medicine.

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