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# The Development of a Formulation of Topical Nanoemulgel of Eberconazole Nitrate

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**KEYWORDS:**
Eberconazole, nano-emulgel, formulation, skin infection

**ABSTRACT**
Eberconazole is used to treat invasive Aspergillus and Candida infections, as well as fungal infections caused by Scedosporium and Fusarium species, which can occur in immunocompromised patients. It is also used to treat oropharyngeal candidiasis (OPC), including OPC unresponsive to itraconazole and/or fluconazole. It is also used to treat invasive infections of Candida, Mucor and Aspergillus species in severely immunocompromised patients. Clinical evidence of its usefulness in the treatment of invasive disease (fusariosis) caused by Fusarium species is limited. It appears to be useful in a murine model of naegleriasis. Antifungal therapy is one of the most effective mechanisms for eradicating a fungal infection to improve quality of life. Systemic treatment is usually indicated for nail infections, extensive skin infections, or those that have not responded to topical treatment. Traditional topical dosage forms cannot maintain or control drug transport on the skin for a long time, so they need longer treatment or must be supplemented with oral treatment. Fungal infections require repeated use of conventional dosage forms over a longer period of time. The emulsifier would facilitate long-term contact of the drug with the skin, and it also has the ability to change the properties of the skin, which improves the local treatment of skin fungal diseases. The strategy is to formulate a drug-loaded Nanoemulgel, which regulates the release of the drug on the skin surface within 24 hours.

**Introduction-**
Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Skin is one of the most readily accessible organs on human body for topical administration and is main route of topical drug delivery system [1].

Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne) or the cutaneous manifestations of a general disease (e.g. psoriasis) with the intent of confining the pharmacological or other effect of the drug to the surface of the skin or within the skin. Topical drug delivery systems include a large variety of pharmaceutical dosage form like semisolids, liquid preparation, sprays and solid powders. Most widely used semisolid preparation for topical drug delivery includes gels, creams and ointments [2].
Most of the topical preparations are meant to be applied to the skin. So basic knowledge of the skin and its physiology function are very important for designing topical dosage form. The skin of an average adult body covers a surface area approximately $2m^2$ and receives about one third of the blood circulating through the body [3].

An average human skin surface is known to contain, on the average 40-70 hair follicles and 200-300 sweat ducts on every square centimetre of the skin. The pH of the skin varies from 4 to 5.6. Sweat and fatty acid secreted from sebum influence the pH of the skin surface. The skin can be considered to have four distinct layers of tissue as shown in figure [4].

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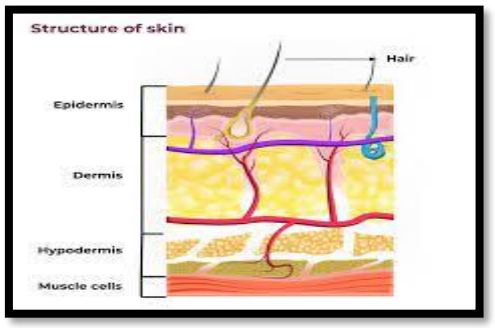


**Fig no 01-** Structure of Skin

**Material –**

The active Eberconazole procure form the Invochem Laboratory. Other ingredient Almond Oil, Polysorbet 80, Propylene Glycol, Carbopol 980 procure for the Arihant ino-chem Industry, Mumbai. Methanol, Ethanol (Absolute) form Research -lab Fine Chem Industry, Mumbai. Potato dextrose Agar form Research -Lab Fine Chem Industry, Mumbai. Potassium dihydrogen phosphate form Research -Lab Fine Chem Industry, Mumbai. Potassium Phosphate (monobasic) form Himedia Lab Pvt. Ltd., Mumbai. Various instrument like FTIR Spectrophotometer with ATR, UV- Visible Spectrophotometer, Brook Field Viscometer, Ultrasonic Bath (Sonicator), Melting Point Apparatus, Melting Point Apparatus used in the research project.

**Formulation and Development of Nanoemulsion-**

**Table no 01-** Composition of Nanoemulsion formulation

| Ingredients | Formulation code | | | | | | |
|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 |
| **Eberconazole %** | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Almond Oil (v/v)** | 3 | 3 | 3 | 2 | 2 | 2 | 1 |
| **Polysorbate 80 (v/v)** | 5.5 | 4.5 | 3.5 | 5.5 | 4.5 | 3.5 | 5.5 |
| **Propylene glycol (v/v)** | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| **Sodium Methyl Paraben (w/w)** | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| **Sodium Propyl Paraben (w/w)** | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 002 | 0.02 |
| **Purified water** | **QS 100** | | | | | | |

**Method of preparation for Nanoemulsion[5,6]-**
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 air oven.

**Preparation of aqueous phase I-**
Accurately weighed quantity of propylene glycol was added into distilled water (80$^0$c).

**Preparation of Oil phase II-**
Weighed quantity of Almond oil and polysorbate 80 mixed by maintaining hot condition, simultaneously accurately weighed quantity of Eberconazole was added into it then addition of methyl paraben, propyl paraben in it.

**Mixing of solution I & II-** Both the phases were mixed properly with the help of High pressure Homogenizer maintaining the respective rpm.

**Preparation of gel [6-10]-**

**Table no 02- Composition of gel**

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

The weighed quantity of carbopol 934 was mixed in distilled water (40$^0$c) further addition of triethanolamine to maintain the desired pH range of the solution. The uniformity in the stirring was maintained and then the gel was kept in the refrigerator for 24 hrs.

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

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**Preformulation Study[11-15]**

**Organoleptic Properties-**

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

**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.

**Ultraviolet - Visible Spectroscopy-**

**Determination of Maximum absorbance: (λ max)**

The UV spectrum of Eberconazole was obtained using UV Shimadzu. Accurately weighed 10 mg of the drug was dissolved in sufficient quantity of methanol. Stock solutions (100 µg/ml) of Eberconazole were prepared in methanol. The UV spectrums were recorded in the range 200-400 nm by using UV-Visible double beam spectrophotometer. The wavelength of maximum absorption ($\lambda_{max}$) was determined.

**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 5000 rpm for30 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.

**Evaluation of Nanoemulsion [16-25]-**

**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.

**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.

**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.

**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 was then diluted appropriately with methanol and estimated using UV visible spectrophotometer at 261 nm.

**Evaluation of Nanoemulsion based Gel [25-35]-**

**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.

**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.

**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 bePolysorbet 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.

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**S = M. L/T**
Where, M = weight tied to upper slide
L = length of glass slides
T = time taken to separate the slides

**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.

**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.

**Result & discussion-**
**Per-formulation study-**
**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 03-** Organoleptic properties of Eberconazole

| **Properties** | **Observed Results** |
|---|---|
| Appearance | Crystalline powder |
| Colour | White |
| Odour | Slight Odour |

**Melting Point-**
The melting point of compound was measured and reported as follows.

**Table no 04-** Melting Point of Eberconazole

| **Drug** | **Observed Value** | **Reported Value** |
|---|---|---|
| Eberconazole | $170^0$c | 170-$172^0$c |

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

**Solubility –**
Solubility of Eberconazole has been tabulated in the following table,

**Table no 05-** Solubility of Eberconazole

| **Solvent** | **Solubility** |
|---|---|
| Methanol | Soluble |
| Water | Slightly soluble |
| Acetonitrile | Soluble |
| 0.1 N HCl | Soluble |
| Phosphate Buffer 6.8 | soluble |

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

**Ultraviolet – Visible Spectroscopy study-**
**Determination of ($\lambda_{max}$) of Eberconazole in Methanol-**
The UV spectrum of Eberconazole solution (100µg/ml) scanned bePolysorbet 400-200 nm using UV spectrophotometer exhibited wavelength of absorbance maxima at 261 nm. λmax of Eberconazole in Methanol.

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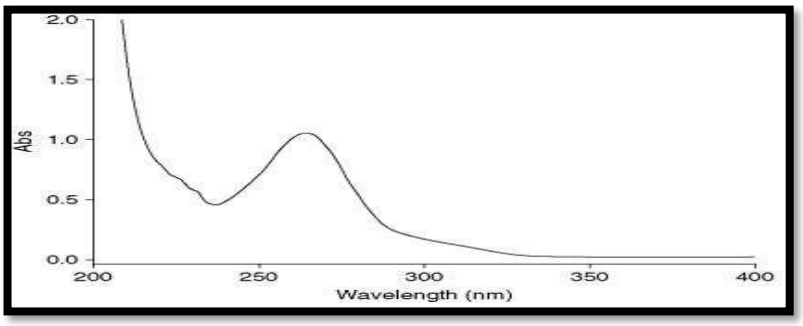


**Fig 02-** UV Spectra of Eberconazole

**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 06-** Calibration Curve of Eberconazole in Methanol

| **Dilations** | **Absorbance** |
|---|---|
| 2 ppm | 0.2031 |
| 4 ppm | 0.385 |
| 6 ppm | 0.551 |
| 8 ppm | 0.728 |
| 10 ppm | 0.903 |

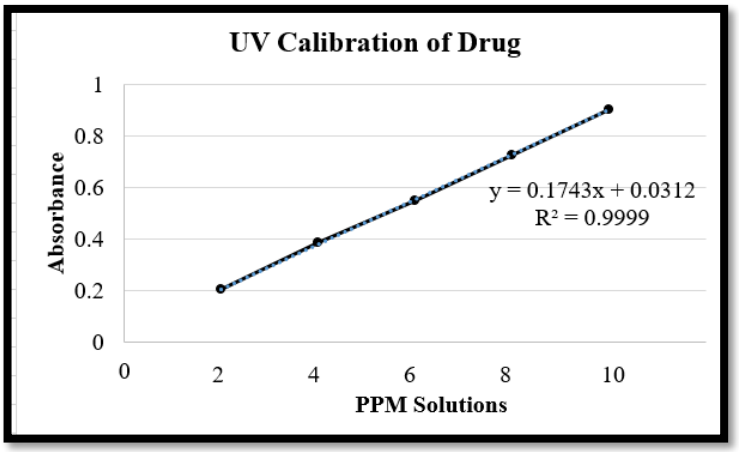


**Fig no 03-** Calibration curve of Eberconazole in Methanol

**Solubility study of drug in different oils-**

**Table no 07-** 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.

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**Evaluation of Nanoemulsion-**

**Entrapment Efficiency-**

The maximum Entrapment efficiency was found to be 96.00% and the minimum Entrapment efficiency was found to be 70.00% in the figure. It has been observed that the drug entrapment efficiency was highest for the optimized batch (F1).

**Table no 08 -** Entrapment efficiency of formulation F1 to F7.

| Formulation code | % Entrapment Efficiency |
|---|---|
| **F1** | 96 |
| **F2** | 95 |
| **F3** | 92.1 |
| **F4** | 90 |
| **F5** | 88 |
| **F6** | 75 |
| **F7** | 75 |

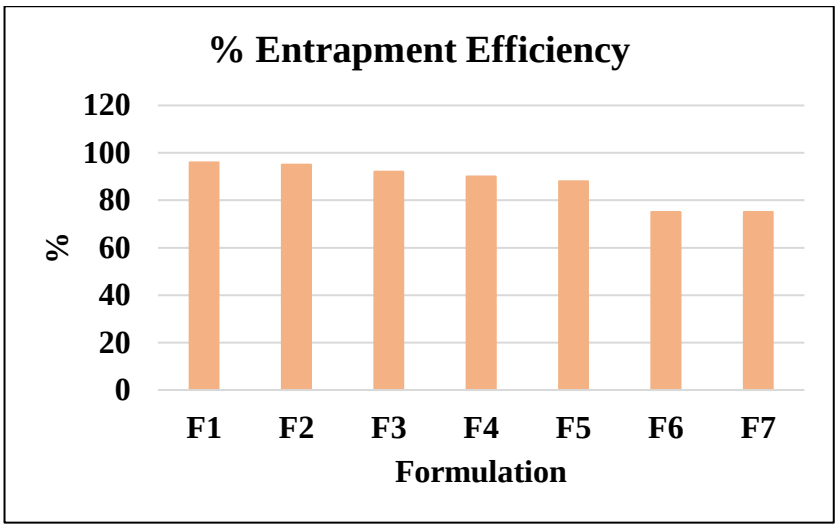


**Fig no 04-** Entrapment efficiency of F1 to F9

**Particle size:**

The Particle size of the Nanoemulsion of optimized 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 09- Size Distribution**

| Formulation code | Particle Size |
|---|---|
| **F1** | 100 |
| **F2** | 120 |
| **F3** | 150 |
| **F4** | 200 |
| **F5** | 270 |
| **F6** | 220 |
| **F7** | 110 |

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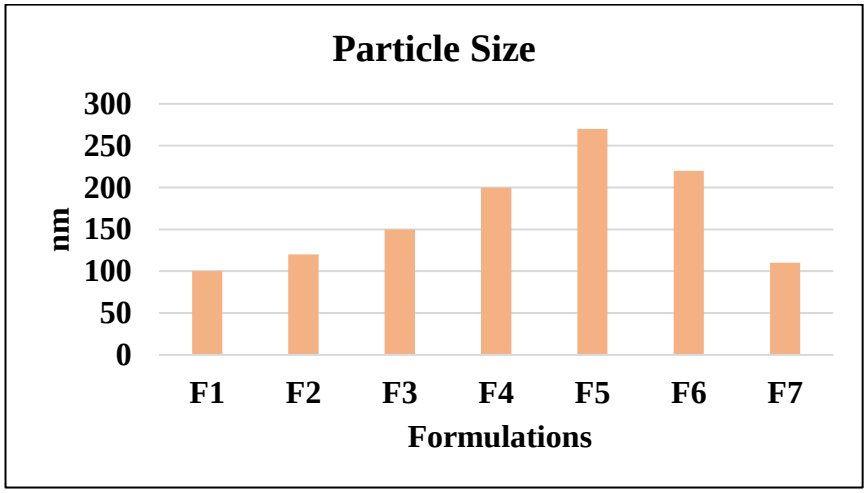


**Fig no 05-** Graph of Particle size of formulations.

**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.

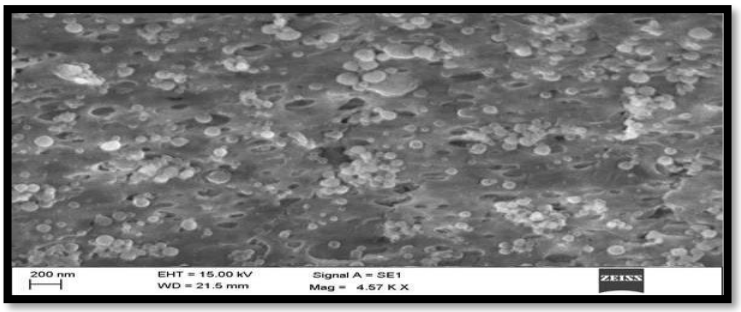


**Fig no 06- Scanning Electron Microscopy**

**Evaluation of Emulgel-**

**Physical appearance-**

**Table no 10-** 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.

**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.

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**Table no 11-** 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 |

**Viscosity -**

The viscosity values of formulations are shown in the following table

**Table no 12-** Viscosity of formulations

| RPM | Formulation Code | | | | | | |
|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 |
| 10 | 14659 | 14025 | 14264 | 14365 | 13655 | 13664 | 13986 |
| 20 | 14102 | 13648 | 14102 | 13787 | 12664 | 12054 | 13264 |
| 30 | 13865 | 12645 | 13841 | 12745 | 12024 | 11546 | 12856 |
| 40 | 12984 | 11652 | 12635 | 11566 | 11654 | 11054 | 12054 |
| 50 | 12325 | 10254 | 11424 | 10325 | 11265 | 9634 | 11856 |

Viscosity is resistance to flow, which is important physicochemical property for topical preparations because it influences Spreadability and drug release as well as jellification. Rheological behavior of the emulgel indicates that the system was shear thinning in nature showing decrease in viscosity at increasing shear rate. The values of viscosity measurement of all formulation are listed in table. This viscosity result resembles that the increase in proportion of Almond oil and increase in speed of homogenizer results in decrease in viscosity.

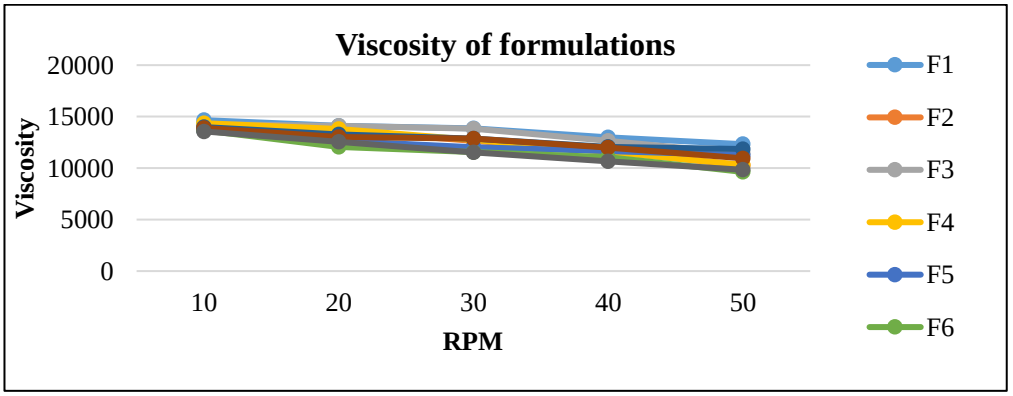


**Fig no 07-** Viscosity of formulation

**Spreadability-**

Spreadability of emulgel is very important in the topical emulgel formulations. Spreadability shows the inverse relationship with the viscosity of the emulgel. Formulation with higher viscosity are very thick in nature, difficult to spread; on the contrary emulgels having very low viscosity have fluid like appearance, both the extremes are not suitable for any of the topical preparation. Hence gel having optimum viscosity provides proper spreadability to the formulations. Formulation F1, Having optimum viscosity and spreadability of this formulation is 18.14 gm.cm/sec.

**Table no-13** Spreadability values of formulation

| Formulation code | Spreadability (g.cm/sec). |
|---|---|
| F1 | 18.14 |
| F2 | 16.02 |
| F3 | 15.45 |
| F4 | 14.26 |

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| | |
|---|---|
| F5 | 15.48 |
| F6 | 14.94 |
| F7 | 16.55 |

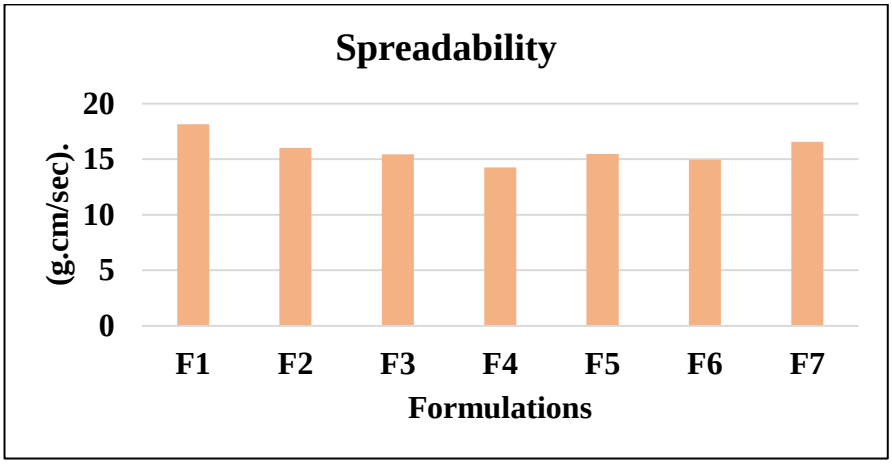


**Fig no 08-** The Graphical representation of Spreadability values of formulation

**Drug Content -**

The drug content of formulation has shown in following table:

**Table no -14** 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 |

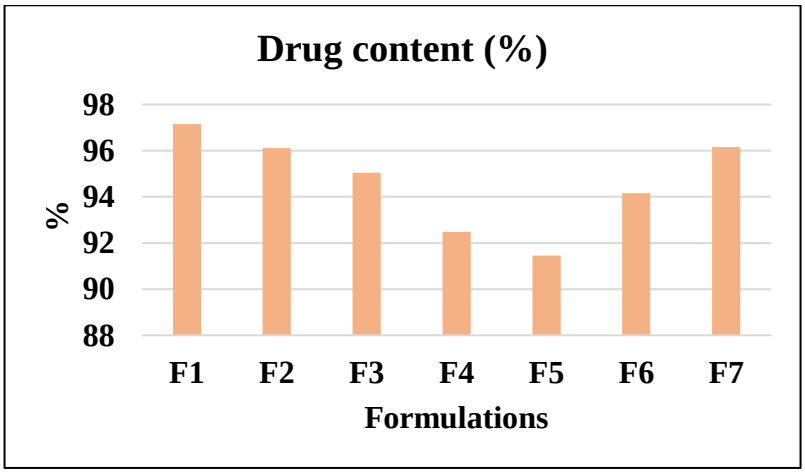


**Fig no 09-** The graphical representation of Drug content.

The percentage drug content of all prepared emulgel formulations was found to be in the range of 91 to 97%. Therefore uniformity of content was maintained in all formulations. The F1 Formulation drug content was found to be 97%.

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**In-vitro drug release study-**

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

**Table no- 15** *in- vitro* release of Eberconazole from its various emulgel formulae

| Time hrs | F1 | F2 | F3 | F4 | F5 | F6 | F7 |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 9.56 | 8.64 | 9.65 | 5.69 | 4.16 | 6.56 | 6.56 |
| 2 | 15.26 | 12.64 | 15.26 | 10.59 | 12.64 | 15.46 | 20.16 |
| 3 | 25.64 | 24.6 | 20.26 | 25.94 | 20.49 | 21.26 | 20.31 |
| 4 | 31.64 | 32.64 | 26.46 | 27.59 | 25.46 | 22.94 | 23.96 |
| 5 | 39.64 | 41.6 | 31.6 | 30.19 | 33.64 | 35.49 | 30.23 |
| 6 | 46.45 | 45.4 | 42.95 | 43.19 | 40.49 | 39.46 | 39.14 |
| 7 | 58.56 | 55.46 | 51.06 | 45.94 | 45.16 | 42.64 | 42.1 |
| 8 | 66.6 | 60.12 | 59.54 | 55.40 | 55.4 | 52.08 | 48.46 |
| 12 | 75.46 | 74.6 | 63.19 | 61.02 | 59.16 | 56.49 | 55.12 |
| 16 | 85.16 | 76..12 | 69.94 | 67.94 | 65.46 | 62.12 | 59.51 |
| 24 | 96.16 | 80.46 | 72.49 | 75.06 | 70.16 | 66.19 | 62.01 |

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

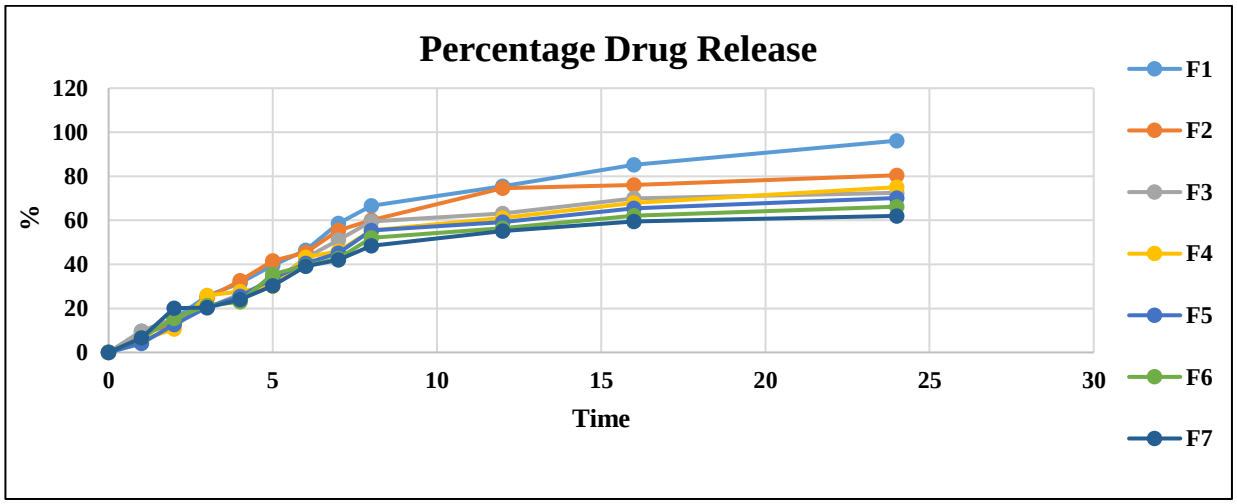


**Fig no 10-** The Percentage Drug Release

**Comparative study-**

**Table no -16** Cumulative drug release of Optimized formulation and Marketed formulation (Ebernet)

| Time(hours) | Optimized formulation | Marketed formulation |
|---|---|---|
| 0 | 0 | 0 |
| 1 | 9.56 | 8.32 |
| 2 | 15.26 | 13.25 |
| 3 | 25.64 | 24.65 |
| 4 | 31.64 | 32.15 |
| 5 | 39.64 | 40.41 |
| 6 | 46.45 | 47.95 |
| 7 | 58.56 | 56.41 |
| 8 | 66.6 | 62.63 |
| 12 | 75.46 | 72.15 |
| 16 | 85.16 | 83.14 |
| 24 | 96.16 | 92.36 |

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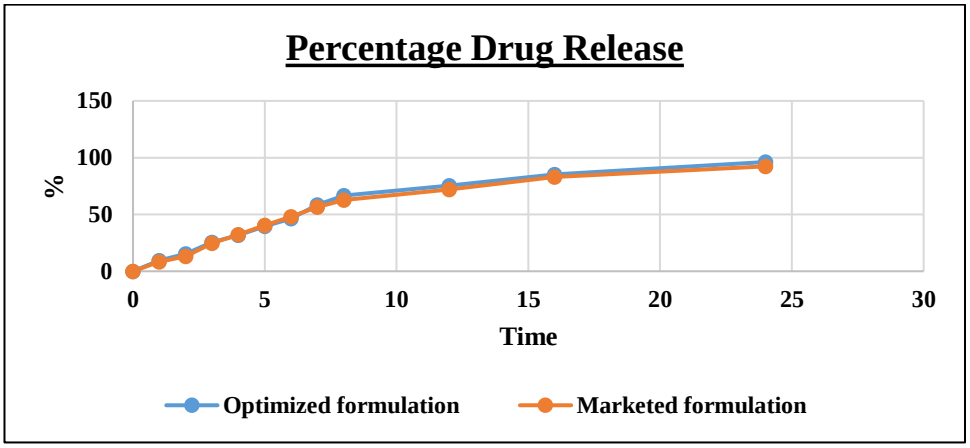


**Fig no 11-** The Comparative percentage drug release of marketed & Optimized formulation

It was observed that the release of the drug from optimized (F1) emulgel formulation was higher than the commercial gel. (0.1 % gel). The drug release of optimised formulation shows the controlled release up to 24 hrs (96 %) and marketed formulation shows (92 %) drug release upto 12 hrs. Formulation F1 showed steady state release upto 24 hours which also indicates that this formulation would show better contact with biological membrane. The drug is entrapped in the oil phase, hence when formulation was applied on egg membrane the penetration takes place upto 24 hrs.

**Conclusion-**

Amongst all the formulations, Nanoemulsion loaded emulgel prepared with the tween 80, Almond oil was found to be better with the drug diffusion. The particle size of optimized formulation (Nanoemulsion) was found to be 131.0 nm which suggest the possible increased penetration of drug through biological membrane. Scanning electron microscopy shows spherical shape and size below micrometer range. Decrease in viscosity value leads to increase in spredability value of all the viscosity results suggest, the suitability of formulation for external use. The percentage of drug content was found to be in 91-96% hence, uniformity of content was maintained. When the optimized formulation was compared with the marketed formulation for in vitro drug release, it was found to have a controlled release of the optimized batch (F1) within 24 hours. And the preparation on the market in 12 hours. A percutaneous mechanism for effective and prolonged treatment, which is necessary for fungal infections and to improve stability

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