Preparation and Evaluation of Eberconazole Nitrate Nanoemulgel for Treatment of Fungal Infections

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Abstract: The objective of this study was to develop a nanoemulgel that would facilitate the topical administration of the antifungal drug eberconazole, which is beneficial in the treatment of fungal infections. Cabopol 934 gelling agent, Almond Oil, Polysorbate 80, Propylene glycol were employed in the eberconazole Nanoemulgel formulation. Diverse parameters were examined in the nanoemulgel that had been prepared. The physical appearance, viscosity, drug release, globule size, scanning electron microscopy, and stability of the nanoemulgel that was prepared were assessed. The formulation F7 exhibited the highest activity, as evidenced by the drug release of 96.16 at 24 hours through a diffusion-controlled mechanism.
Comparative analysis of Optimized formulation F7 and Marketed formulation (Ebernet) investigated and revealed that the drug was released at a higher rate from the enhanced (F7) emulgel formulation than the commercial gel. The gel contains 0.1% concentration. With a release rate of 96%, the perfected formulation shows regulated drug release for up to 24 hours. By contrast, the marketed formulation shows drug release of 92% for up to 12 hours. Consistent release over a 24-hour period shown by Formulation F7 suggests enhanced contact with the cellular membrane.

Keywords: Eberconazole Nitrate, Nanoemulgel, Topical drug delivery.

I. INTRODUCTION

The topical medication delivery technique is often used to treat skin infections, such as fungal infections. A topical drug delivery system refers to a targeted method of delivering medicine to the skin in order to provide a localized therapeutic impact for treating skin disorders. Topical medication delivery systems have been used for the treatment of both dermatological and cosmetic conditions, targeting either diseased or healthy skin. Topical formulations provide many benefits, including the avoidance of hazards and inconveniences associated with intravenous treatment, as well as the ability to bypass absorption challenges such as pH fluctuations, presence of enzymes, and stomach emptying time[1]. The restricted dermal and transdermal transport of many tiny and big molecules is a significant difficulty because of the stubborn barrier qualities of the skin. Emulsion is a dispersed system made up of evenly spaced tiny droplets in an immiscible medium[2]. Nanoemulsion system integrated into the hydrogel matrix, which improves skin penetration, nanoemulgel is defined as the creation of hydrogel based on nanoemulsion[3]. Nanoemulsion offers a viable solution for enhancing the penetration and targeting of poorly soluble pharmaceuticals in drug delivery systems. It does this by increasing the absorption of the medication through the skin, improving the retention period of the drug in the target region, and ultimately reducing the occurrence of adverse effects[4].

The advantages of nanoemulsion, which contains globules of nano-scale size, are not dependent on the physical features of the emulsion itself[5]. Instead, they enhance the bioavailability of therapeutic medications as a whole. Research has shown that the bioavailability of lacidipine via the transdermal route is 3.5 times more than that of the oral route. This is considered to be because the transdermal route avoids first-pass metabolism[6].

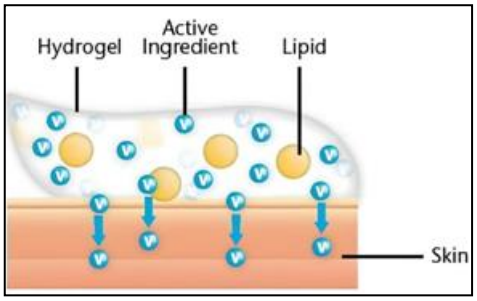

Fig 1: Structure of Emulgel

Mechanism of Permeation Enhancer[7]

Enhancers modify the nanostructure of the stratum corneum's lipid matrix, increasing permeability. Fatty acid enhancers improved fluidity in the lipid protein layer of the stratum corneum. Enhancers can affect both polar and non-polar pathways by modifying the multi-laminated channel for penetration. Enhancers can improve drug diffusion through skin proteins. The choice of enhancer greatly influences product design and development.

Penetration enhancers can function through three basic mechanisms[8]:

- Disruption of the highly ordered structure of stratum corneum lipid.
- Interaction with intercellular protein.
- Improved partition of the drug, co- enhancer or solvent into the stratum corneum. Terpenes, which improve drug diffusion by removing lipids from the stratum corneum, demonstrate reorganization of the lipid domain and barrier disruption.

II. MATERIALS AND METHODS

Eberconazole was a gift sample obtained by Festiva Pharma, Gujarat, carbopol 934 & Potassium dihydrogen phosphate was obtained from Loba chemie pvt ltd, Mumbai, Sodium methyl paraben & Propyl paraben obtained from Alta labs, Mumbai and all other chemicals & reagents were of SD fine chemicals provided by the college.

Preparation of Nanoemulsion[9]:

Preparation of Aqueous Phase: Weighed quantity of propylene glycol is added into distilled water maintained at 80°C and Stirred until the solution became homogeneous by using a magnetic stirrer with a hot plate.

Preparation of Oil Phase: Weighed quantities of almond oil and polysorbate 80 were mixed by maintaining the mixture at a hot condition using a water bath & accurately weighed quantity of Eberconazole was added along with methyl paraben and propyl paraben to the mixture and Stirred until all components are thoroughly mixed and dissolved using a magnetic stirrer with a hot plate.

Mixing of Aqueous and Oil Phases: Aqueous phase and oil phase were mixed using a magnetic stirrer for initial mixing, after mixing the mixture was transferred to a high-pressure homogenizer (5000 to 15000 psi) to form a fine nanoemulsion. Homogenization was continued until the desired droplet size in the range of 20-200 nm was achieved.

Preparation of Nanoemulgel:

Required quantity of carbopol 934 is weighed and mixed it in distilled water maintained at 40°C, triethanolamine was added to adjust the pH to the desired range, stirred the mixture uniformly by magnetic stirrer. Incorporated nanoemulsion containing drug into the gel base. Mixed thoroughly to ensure uniform distribution of the nanoemulsion within the gel.

Table 1: Formulation Table

Ingredietns	F1	F2	F3	F4	F5	F6	F7
Eberconazole %	1	1	1	1	1	1	1
Almond oil (v/v)	1	2	2	2	3	3	3
Polysorbate 80 (v/v)	5.5	3.5	4.5	5.5	3.5	4.5	5.5
Propylene glycol (v/v)	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Sodium Propyl paraben (w/w)	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Sodium methyl paraben (w/w)	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Purified water (q.s ml)	100	100	100	100	100	100	100

III. RESULTS & DISCUSSION

Entrapment Efficiency: The maximum Entrapment efficiency was found to be 96% and the minimum Entrapment efficiency was found to be 70%. It has been observed that the drug entrapment efficiency was highest for the optimized batch (F7). The significantly higher entrapment efficiency of F7 (96%) compared to other formulations suggests a superior ability to retain the active drug within the formulation matrix.

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. The reduction in particle size to around 100 nm in the F7 formulation plays a pivotal role in enhancing drug delivery.

Table 2: % entrapment efficiency & Particle size of all the formulations

Formulations	% entrapment efficiency	Particle size
F1	75	110
F2	75	220
F3	88	270
F4	90	200
F5	92.1	150
F6	95	120
F7	96	100

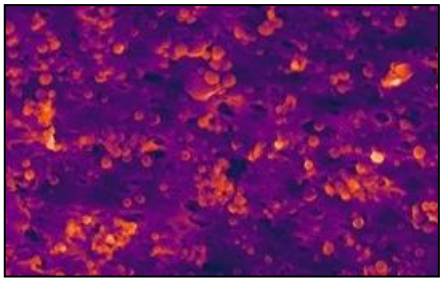

Fig 2: SEM of Nanoemulsion

Scanning Electron Microscopy: The shape of Nanoemulsion was Spherical which is seen in reddish orange colour. Moreover, the micrograph also revealed some agglomeration of nanoemulsion which might be due to the evaporation of water present in formulation during sample preparation prior to SEM analysis.

Viscosity: Viscosity is resistance to flow, important physicochemical property for topical preparations because it influences Spreadability and drug release as well as jellification. Rheological behaviour of the emulgel indicates that the system was shear thinning in nature showing decrease in viscosity at increasing shear rate.

Table 3: Viscosity of prepared formulations

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

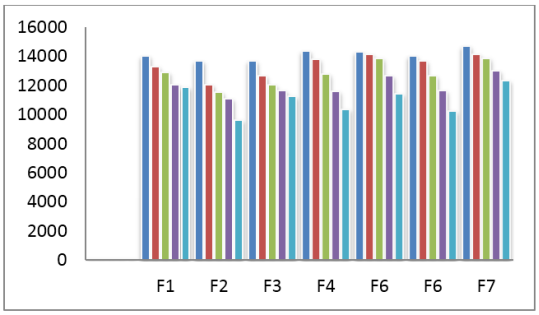

Fig 3: Bar graph of viscosity for prepared formulations

Spreadability: The spreadability of emulgel is very important in the topical emulgel formulations. Spreadability shows an inverse relationship with the viscosity of the emulgel. Formulation with higher viscosity is 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 F7, having optimum viscosity and spreadability of this formulation is 18.14 gm.cm/sec.

In-vitro drug release study: The controlled release profile of F7, with 96% drug release over 24 hours, is a significant improvement over the marketed formulation, which released 92% of the drug in just 12 hours. This controlled release is advantageous as it ensures a prolonged therapeutic effect, reducing the need for frequent reapplication and enhancing patient compliance. The slower release rate may also contribute to a more sustained antifungal action, which is critical in treating infections.

Table 4: In-vitro drug release of all the formulations

Time in hrs	F1	F2	F3	F4	F5	F6	F7
1	6.56	6.56	4.16	5.69	9.65	8.64	9.56
2	20.16	15.46	12.64	10.59	15.26	12.64	15.26
3	20.31	21.26	20.49	25.94	20.26	24.6	25.64
4	23.96	22.94	25.46	27.59	26.46	32.64	31.64

5	30.23	35.49	33.64	30.19	31.6	41.6	39.64
6	39.14	39.46	40.49	43.19	42.95	45.4	46.45
7	42.1	42.64	45.16	45.94	51.06	55.46	58.56
8	48.46	52.08	55.4	55.4	59.54	60.12	66.6
12	55.12	56.49	59.16	61.02	63.19	74.6	75.46
16	59.51	62.12	65.46	67.94	69.94	76.12	85.16
24	62.01	66.19	70.16	75.06	72.49	80.46	96.16

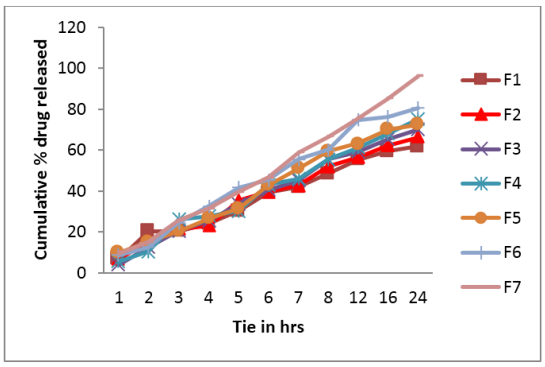

Fig 4: In-vitro drug release curve for all the formulations

Comparative study: Comparative study of Optimized formulation F7 and Marketed formulation (Ebernet) using Cumulative drug release parameter was performed F7 outperformed in terms of drug diffusion and penetration. The study highlights the role of almond oil in improving the formulation's properties, suggesting that the choice of oil in the nanoemulsion is critical to achieving optimal results.

Table 5: Comparative study of Optimized formulation F7 and Marketed formulation

Time in hrs	Optimized formulation F7	Marketed formulation
1	9.56	8.37
2	15.26	13.3
3	25.64	24.7
4	31.64	32.2
5	39.64	40.46
6	46.45	48
7	58.56	56.46
8	66.6	62.68
12	75.46	72.2
16	85.16	83.19
24	96.16	92.41

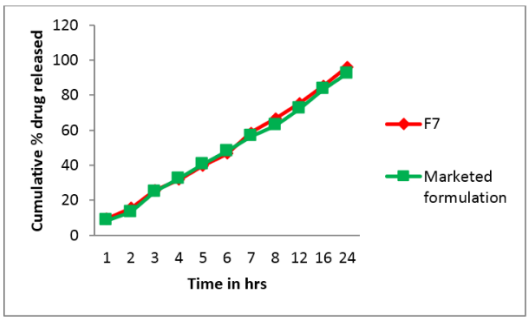

Fig 5: Comparative study of Optimized formulation F7 and Marketed formulation (Ebernet)

Stability Studies: The stability study results show that the cumulative drug release from the formulations remained highly consistent over 1, 30, 60, and 90 days. On day 1, the release ranged from 19.24 ± 0.76% at 1 hour to 97.66 ± 0.35% at 24 hours. This profile was maintained across all time points, with negligible variations after 30, 60, and 90 days. The formulations consistently released the drug efficiently, with minimal changes, even after extended storage. These results demonstrate the excellent stability of the formulations, ensuring reliable therapeutic performance over time.

Table 6: InVitro Drug Release data of the formulation F7

Time (Hrs)	Cumulative Percent drug released ± SD		
	40^0±2°C & 75%±5% RH		
	1st day	60th day	90th day
2	19.24	18.6	18.1
4	25.22	25	24.15
6	35.8	34.5	34.1
8	44.67	43.81	43.2
10	60.6	59.7	58.8
12	66.11	65.5	64.7
16	74.26	73.77	73.1
18	85.98	84	84.7
20	90.35	89.2	88.6
22	96.9	96.3	95.3
24	97.66	96.1	95.9

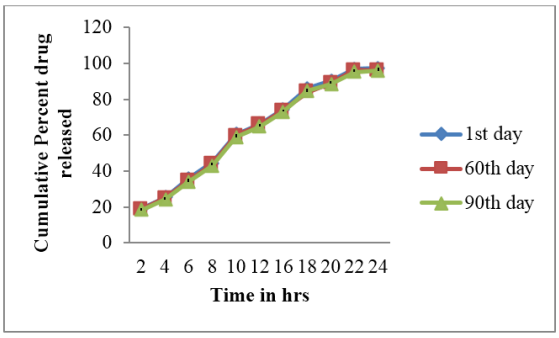

Fig 6: InVitro Drug Release curves of formulation F7

IV.CONCLUSION

- Out of all the formulations, the drug diffusion was determined to be better with almond oil-prepared Nanoemulsion loaded Emulgel than with Tween 80.
- All of the viscosity findings indicate that the formulation is suitable for exterior usage when the viscosity value decreases and the spreadability value increases.
- It was discovered that the optimized batch (F7) had a regulated release within 24 hours when the improved formulation for in vitro drug release was compared with the marketed formulation.

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