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RESEARCH ARTICLE

DESIGN, DEVELOPMENT AND EVALUATION OF MICROEMULGEL CONTAINING ECONAZOLE NITRATE

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ABSTRACT

The study was designed with the aim to evaluate Econazole nitrate Microemulgel for a treatment of fungal infection. Microemulgel is isotropic mixtures of oil, water and emulsifying agent. Recently, Microemulgel has emerged as one of the most interesting topical preparation in the field of pharmaceutical sciences. The use of Microemulgel as a delivery system has several advantages such as ease of administration, increased residence time of drug at applied site, better drug release, good thermodynamic stability and higher transdermal permeability over conventional formulation. The objective of the study was to prepare Microemulgel of Econazole nitrate, using Carbopol 940 and HPMC [9004-65-3] as a gelling agent, oil phase, preservative, emulsifying agent and buffers was used as penetration enhancer. All the prepared Microemulgel formulations showed acceptable physical properties, appearance, spreadability, homogeneity, viscosity, pH, and Formulations were tested for drug excipient interactions subjecting to FTIR Spectral analysis, Skin irritation test, In-vitro drug diffusion studies showed 98.89% for F9 formulation maximum release of drug in 120 minutes and Stability Studies. The clinical evaluation proved the efficacy and tolerability of this preparation in the treatment of various topical fungal infections. Topical antifungal treatment was successfully achieved with Econazole nitrate microemulgel.

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INTRODUCTION

Topical therapy has been used for centuries for the treatment of fungal infection. The spectrum of drugs/agents applied directly to the skin ranges from anti inflammatory, antiseptic, antibacterial, antifungal, antiviral, anti-acne, anti-pigmentary, anesthetic compounds to skin emollients and protectants. Topical route has the main advantage of direct delivery of drug to the target tissue i.e. skin and mucous membranes, by passing the firs-pass effect. However, skin permeation of a drug moiety from topical formulation is a multi-step process. The formulation and development of novel drug delivery system with the nature of enhancing the effectiveness of existing of drug is an ongoing process in pharmaceutical research. The concept of microemulsion was first introduced by Hoar and Schulman during 1940s. While microemulgel is the combined form of microemulsion and gel have advantage of both. In recent year the focus of pharmaceutical researches gradually shifting to the development of drug delivery systems rather than finding newer chemical entities for an around improve mentation drug therapy. Over the last decades the treatment of illness has been carry out by administrating drug to human body via various routes namely oral, sublingual, rectal parental etc. when these systems are fail to administration of drug that time use topical drug delivery system. Topical drug delivery system define as the application of drug containing formulation directly to the skin to treat cutaneous disorder with the intent of containing the pharmacological or other effect of the drug to the surface of the skin. Now a day's scenario pharmaceutical researches work is focused to fulfill the therapeutic needs of patients. Most widely used drugs when given by oral route have side effects like gastric irritation, nausea, bleeding in gastrointestinal tract etc. In order to minimize such side effects and systematic toxicities and also achieve better therapeutic effects one of the promising method is to administered drug via skin or, in short by topical drug delivery system. Gels as topical drug delivery system possess a number of advantages like ease of application, less greasy and easily removed. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation microemulgel are prepared and with their use even a hydrophobic drug can enjoy the unique properties of gel. Microemulgel are the combination of microemulsion and gel. In recent years there has been great interest in the use of novel polymers with complex functions as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing

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surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase. In fact, the presence of a gelling agent in the water phase converts a classical microemulsion in to a microemulgel. Both oil-in-water and water-in-oil emulsions are extensively used as vehicles to deliver various hydrophilic as well as hydrophobic drugs to the skin in microemulgel formulation. They similarly have attainment to dissolve drug and to penetrate the skin. Oil-in-water emulsions are mostly useful as water washable drug bases and for general cosmetic purposes, while water-in-oil emulsions are employed more widely for the treatment of dry skin and emollient application. Gel formulations generally provide faster drug release as compared to other semisolid dosage forms. When microemulgel are used for dermatological motive then microemulgel have several favorable properties such as it should be thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, water-soluble, longer shelf life, bio-friendly, transparent and pleasing appearance. Emulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate the skin microemulgel have a higher aqueous component which permits greater dissolution of drugs and also permit easy migration of the drug through a vehicle that is essentially a liquid.

Drug delivery across the skin (Surender Kumar, 2015; Dadwal Meenakshi Emulgel, 2013): The epidermis is the most superficial layer of the skin and is composed of stratified keratinized squamous epithelium which varies in thickness in different parts of the body. It is thickest on with elastic fibers. The skin forms a relatively waterproof layer that protects the deeper and more delicate structures. Blood vessels are distributed profusely beneath the skin. Especially important is a continuous venous plexus that is supplied by in flow of blood from the skin capillaries. In the most exposed areas of the body hands, feet, and ears blood is also supplied to the plexus directly from the small arteries through highly muscular arteriovenous anastomosis. A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment. The skin acts as a two way barrier to prevent absorption or loss of water and electrolytes. There are three primary mechanisms of topical drug absorption:

Transcellular, intercellular and follicular. Most drugs pass through the torturous path around corneocytes and through the lipid bilayer to viable layers of the skin. The next most general route of delivery is via the pilosebaceous route. The barrier resides in the outermost layer of the epidermis, the stratum corneum, as evidenced by approximately equal rates of penetration of chemicals through isolated stratum corneum or whole skin. Creams and gels that are rubbed into the skin have been used for years to deliver pain medication and infection fighting drugs to an affected site of the body. These include, among others, gels and creams for vaginal yeast infections, topical creams for skin infections and creams to so the arthritis pain. New technologies now allow other drugs to be absorbed through the skin (transdermal). These can be used to treat not just the affected areas (for example, the skin) but the entire body.

Microemulgel (Banker and Rodes, 1979; Vikas Singla, 2012; Shaik, ?): When microemulsion and gel are used in combination dosage forms the prepared formulations are known as Microemulgel. Microemulgel having the advantages of both gel as well as microemulsion. Both hydrophobic and hydrophilic types of drugs are incorporated into dosage forms. Microemulgel provide a large surface area for drug absorption and oil portion increases the bioavailability by improving permeability of drugs. The stability of microemulsion is increased when it is incorporated in to the gel. As compared to microemulsion, microemulgel have a certain degree of elegance and easily washable at any time required.

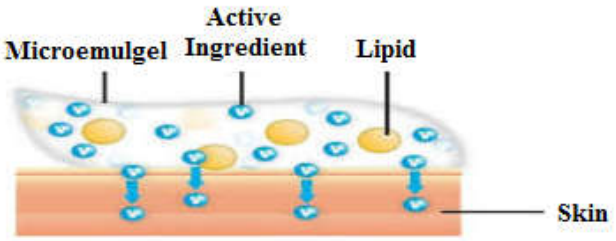

Figure 1. Structure of Microemulgel

MATERIALS AND METHODS

Materials

Econazole nitrate was received as a gift sample from Supriya Life Science Ltd., Mumbai. India. Carbopol-940, HPMC [9004-65-3], Propylene glycol, Polyethylene Glycol, Methyl Paraben, Propyl Paraben was received from Ozone International Mumbai, India. DMSO, Glycerin and Triethanolamine were obtained from H.D. Lab Chm. Aurangabad respectively. All other materials and chemicals used were of either pharmaceutical or analytical grade.

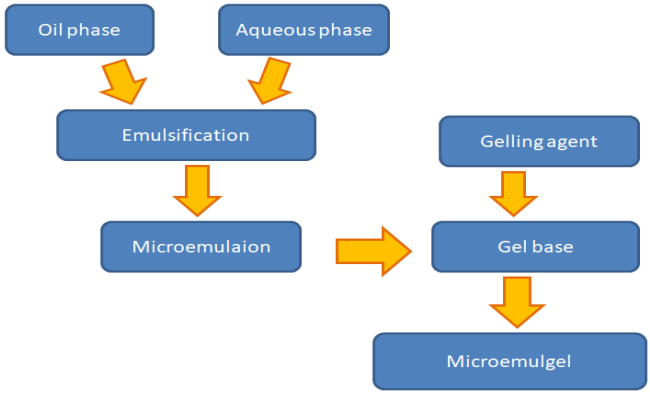

Figure 2. Formulations flow chart

Formulations and Development (Amidon, *et al.,* 1995)

Preparation of Microemulgel of Econazole nitrate: The composition of Microemulgel was established in our earlier study, which consists of Propylene glycol, DMSO, Carbopol, HPMC, Polyethylene glycol, glycerin, methyl paraben, Propyl paraben respectively containing Econazole nitrate (1gm). The microemulsion formulations were prepared Econazole nitrate (1 gm) was dissolved into the mixture of oil, emulsifying agent. The resultant mixture was put in the Ultrasonicater until a clear solution was obtained.

Evaluation parameter (Swapnil Suresh Walekar *et al.,* 2014; Anu Hardenia *et al.,* 2014; Chuah Chong Wooi, 2012; Joshi Baibhav *et al.,* 2011; Peneva *et al.,* 2014**)**

Table 1. Formulation of Microemulgel

Ingredient	Batch code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Econazole nitrate (gm)	1	1	1	1	1	1	1	1	1
Carbopol-940 (gm)	1.4	1.5	1.6	-	1	3.3	3.5	3.7	3.9
HPMC[9004-65-3] (gm)	1	1.1	1.2	3.0	2.1	-	-	-	-
DMSO (ml)	2	3	4	2.5	3.5	4.5	3	4	5
Polyethylene Glycol-40 (ml)	5	5	5	5	5	5	5	5	5
Proplyne Glycol (ml)	6	6	6	6	6	6	6	6	6
Methyl Paraben (mg)	300	300	300	300	300	300	300	300	300
Propyl Paraben (mg)	150	150	150	150	150	150	150	150	150
Glycerine (ml)	5	5	5	5	5	5	5	5	5
Triethanolamine (ml)	0.350	0.400	0.450	0.350	0.400	0.450	0.350	0.400	0.450
Distilled Water (ml)	Up to 100	Up to 100	Up to 100	Up to 100	Up to 100	Up to 100	Up to 100	Up to 100	Up to 100

Table 2. Interpretation of FTIR Spectra of Econazole nitrate + Carbopol and DMSO

Peak assign with peak no.	Standard frequency(cm-1)	Observation frequencies (Econazole nitrate + Carbopol)	Observation frequencies (Econazole nitrate + DMSO)
Imidazole ring C-N stretching	3150-3460	3173.25	3426
C-H aromatic stretching	3000-3150	3108.90	3109
C-H aliphatic stretching	1400-1500	1447	1491.95
C-C bond stretching	1490-1600	1583.73	1585
C-C bond of bending	1400-1490	1488.05	1547
Stretching in C-O-C group	1000-1340	1089.69	1330
P-disubstitued benzene ring	800-860	826.02	825
O-disubstitued benzene ring	750-790	786	781

Table 3. Interpretation of FTIR Spectra of Formulation of Microemulgel

Peak assign with peak no.	Standard frequency(cm-1)	Observation frequencies (API)	Observation frequencies (Formulation)
Imidazole ring C-N stretching	3150-3460	3206.94	3173.43
C-H aromatic stretching	3000-3150	3146.04	3001.05
C-H aliphatic stretching	1400-1500	1492.01	1488.37
C-C bond stretching	1490-1600	1561	1567.69
C-C bond of bending	1400-1490	1488.37	1492.01
Stretching in C-O-C group	1000-1340	1170.38	1194.03
P-disubstitued benzene ring	800-860	825.99	846.03
O-disubstitued benzene ring	750-790	770.79	761.19

Physical appearance: Microemulgel can be tested for their visual appearance, consistency, grittiness and phase separation. The formulations can be tested for their homogeneity by visual appearance after the Microemulgel was applied as a thin layer on the slide.

pH: The pH value of Microemulgel formulation can be measured by using pH meter (Digital pH meter). The pH meter was calibrated with standard buffer solution having pH 4 and 7 before use. And then the 1% aqueous solution of the prepared Microemulgel can be made. 1 gm of formulation was dissolved in distilled water and stirred until it forms uniform suspension, kept it aside for 2 hr. The volume made up to 100 ml and pH of the suspension can be measure with the digital pH meter. The measurements of pH of each formulation were performed in triplicate.

Appearance of Microemulgel: The appearance of the formulations was determined by visual examination of the formulations under light.

Where + average, ++ good, +++ excellent

Spreadability: Spreadability was measured using the spreadability apparatus. The apparatus consists of two slides in which one slide is firmly fixed in a wooden frame while the other slide can easily slide over the surface of the fixed one. An excess of Microemulgel (1 gm) was placed between the two slides of the apparatus. A weight of 1Kg was allowed to rest on the slide for 5 minutes so that a uniform film of Microemulgel was formed and the air between the slides was expelled. The excess gel was removed carefully from the edges of the slides. The bottom slide was properly anchored and the top slide was subjected to a poll of 80 gm weight. The time (in seconds) required by the top slide to cover a distance of 5 cm be noted. A shorter interval indicates better Spreadability.

Spreadability was then calculated using the following formula:

$S = M \times L / T$

Where, S = is the spreadability,

M = is the weight in the pan (tied to the upper slide),
L = is the length moved by the glass slide and
T = represents the time in seconds taken to separate the slide completely.

Rheological study

Brookfield programmable DVII+ Model pro II type viscometer was used for rheological studies. The prepared microemulsion formulations (100 ml) were placed in a beaker and were allowed to equilibrate for 5 minutes before measuring the dial reading using spindle No. 63 for F4 and F8 formulations. The viscosity of plain gel and MBGs were determined at different angular velocities and averages of two reading were used to calculate the viscosity.

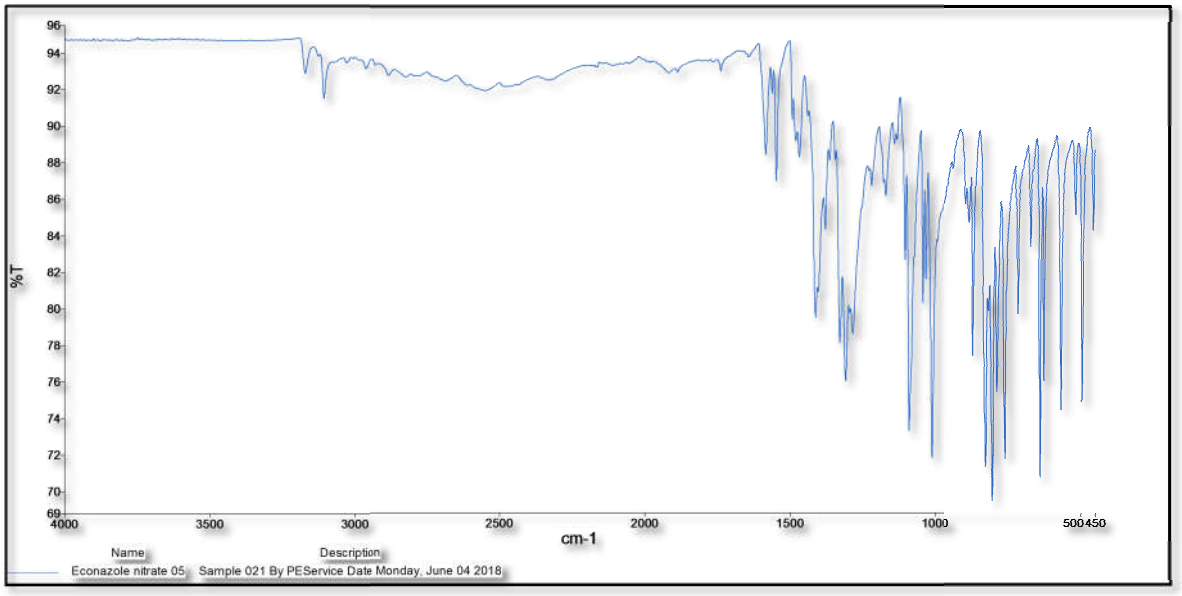

Figure 4. Econazole nitrate (API)

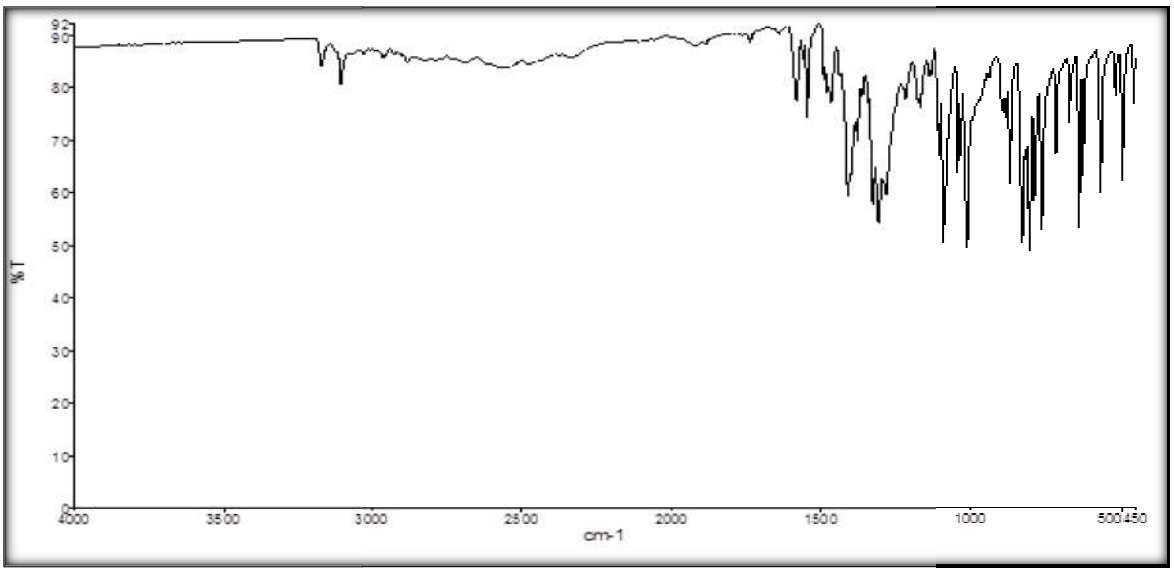

Figure 5. Econazole nitrate + Carbopol

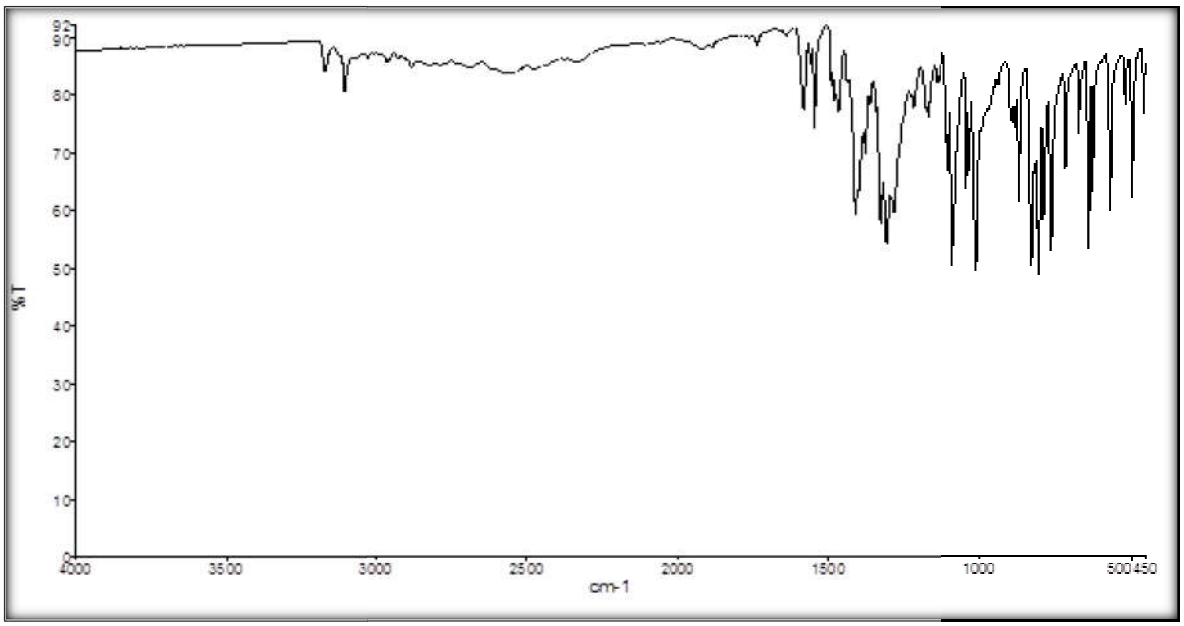

Figure 6. Econazole nitrate + DMSO

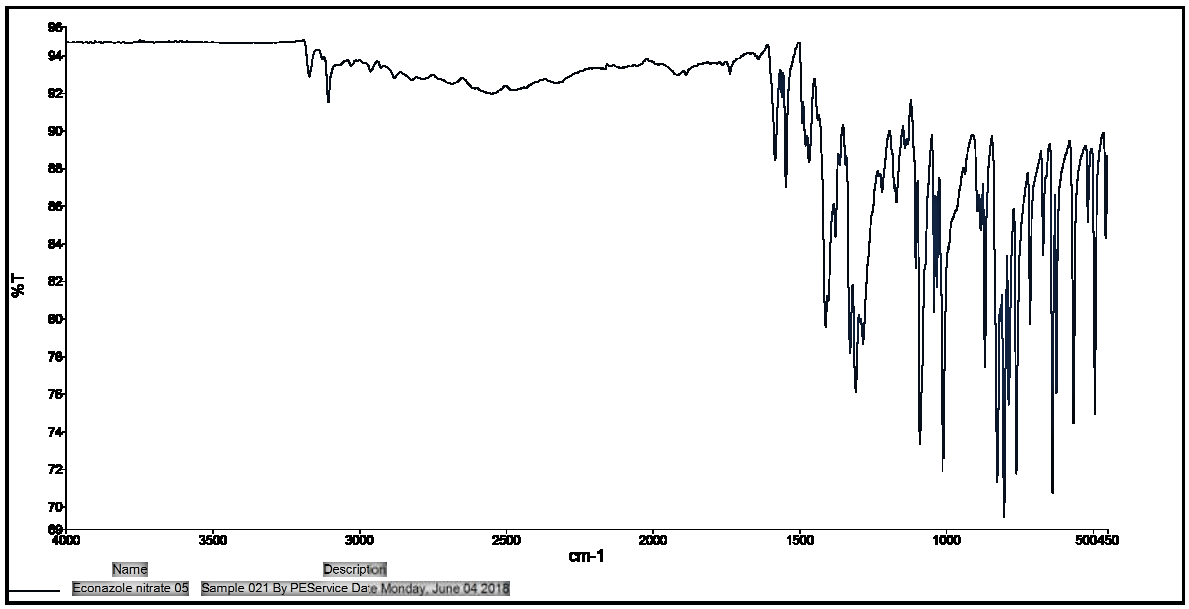

Figure 7. Formulation of Microemulgel

Table 4. Evaluation parameters

Formulation	Color	pH	Consistency	Viscosity	Spreadability
F1	white	6.8	Good	11200	36.45
F2	white	5.9	excellent	14100	54.89
F3	white	6.2	excellent	12600	41.72
F4	white	5.8	Good	13750	36.59
F5	white	6.7	Good	13200	51.75
F6	white	5.7	excellent	17400	31.12
F7	white	6.5	excellent	10800	32.13
F8	white	5.9	Good	11700	49.88
F9	white	6.3	Good	16100	57.73

Table 5. Accelerated stability study

Batch Code	color	pH	consistency	homogeneity	spreadability	% drug release
F9 before stability	white	6.3	Good	16100	57.73	98.89
F9 After Stability	white	6.2	Good	16080	57.03	96.66

Table No. 6: In-vitro diffusion study of Econazole nitrate of batches F1-F9

Time (min)	% drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
15	11.77	12.13	10.71	14.65	12.13	13.70	14.65	16.68	17.80
30	23.11	21.82	19.43	24.81	23.30	24.31	24.81	24.82	26.87
45	32.63	29.64	28.40	32.82	33.80	36.85	33.61	37.19	38.50
60	44.55	39.25	38.55	44.18	44.54	47.40	47.65	52.42	52.84
75	52.37	48.40	50.46	56.47	55.49	58.29	58.89	62.26	63.69
90	61.96	59.80	61.18	64.63	65.72	67.38	72.81	73.11	75.60
105	72.26	69.84	71.03	73.01	76.10	78.95	84.41	85.48	87.88
120	81.03	80.72	82.56	83.16	85.67	87.85	91.88	95.73	98.89

FTIR: FTIR studies were carried out for detection of drug excipient interaction in the present IR study of pure drug Econazole nitrate, Carbapol-940, DMSO, polyethylene Glycol, propylene glycol, methyl paraben and propyl paraben.

Skin Irritation Studies

There is no Erythma or Edema Found on Rat Skin.

Stability study: The stability study conducts by ICH (International Conference on Harmonization) guideline. It showed No significance change in properties of the optimized formulation and the drug release. Short term stability studies were performed in a Stability chamber over a period of 3 months on the promising microemulgel formulation F9. Sufficient number of microemulgel formulations were packed in container or tube and kept in a Stability chamber at temperature 45^0C and RH 75%. Samples were taken on 3 months for colour, PH, consistency, homogeneity, spreadability and in-vitro diffusion studies were performed to determine the drug release profile.

In vitro drug release study: The diffusion medium used was phosphate buffer pH 7.4. Assembly of diffusion cell for in–vitro diffusion studies the diffusion cell was designed as per the dimension given. Diffusion cell with an effective diffusion area of 3.14 cm^2 was used for in vitro permeation studies. The diffusion cells were placed on the magnetic stirrers. The donor compartment consisting of 1 g of microemulgel containing Econazole nitrate.

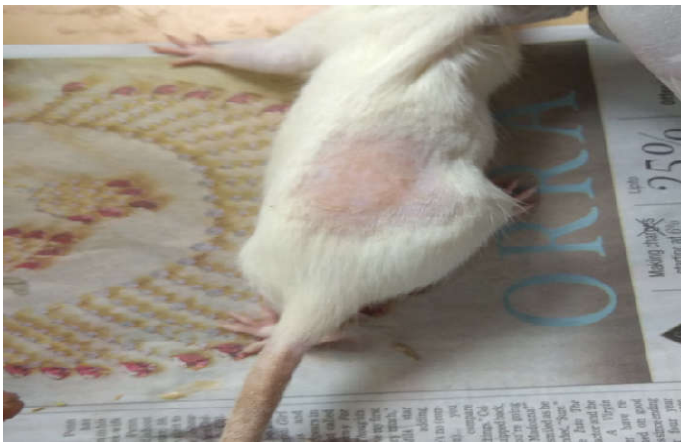

Figure No.8: Wistar rat skin after microemulgel apply on the skin

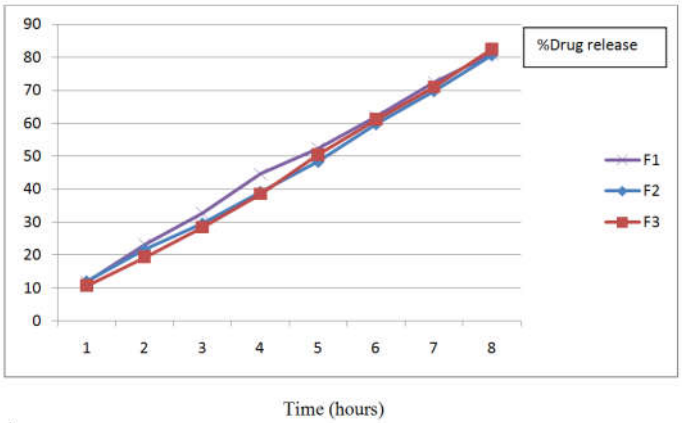

Figure No. 10: In- vitro diffusion study Econazole nitrate of batches F1-F3

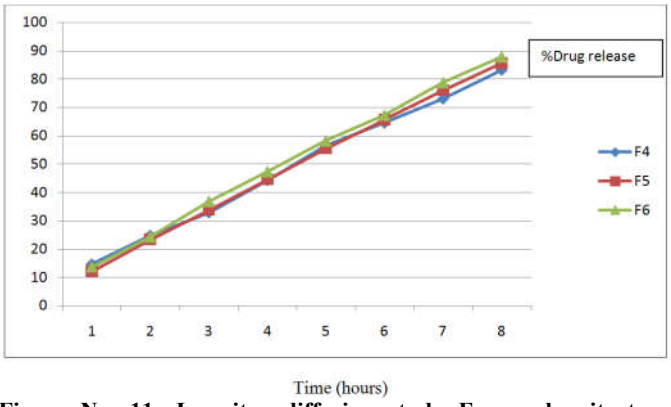

Figure No. 11: In- vitro diffusion study Econazole nitrate of batches F4-F6

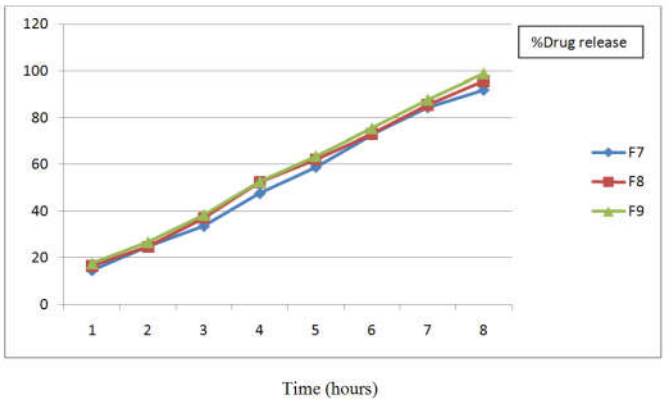

Figure No. 12: In- vitro diffusion study Econazole nitrate of batches F7-F9

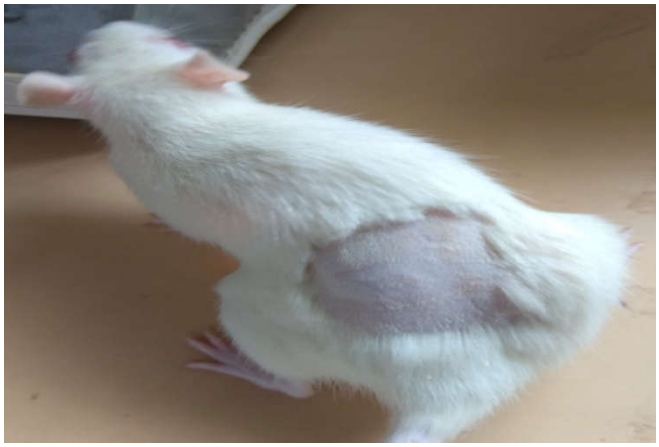

Figure No.9: Wistar rat skin study after 24hrs microemulgel apply on the skin

The receptor compartment was filled with fluid. Then the membrane filter was mounted on the cell carefully so as to avoid the entrapment of air bubble under the chicken membrane. Intimate contact of chicken membrane was ensured with receptor fluid by placing it tightly with clamp. The speed of the stirring was kept constant throughout the experiment. With the help of 1ml pipette 1ml of sample was withdrawn at a time intervals of 30 minutes from sampling port of receptor compartment and same volume was the replaced with receptor fluid solution in order to maintain sink condition. The samples were appropriately diluted and the absorbance was measured at 259 nm using UV visible spectrophotometer.

DISCUSSION

In the present study an attempt has been made to prepare Econazole nitrate Microemulgel formulation using Carbopol 940, HPMC[9004-65-3], propylene glycol, polyethylene glycol, DMSO, methyl paraben, propyl paraben and glycerin. The formulation F9 shows maximum release up to 98.89 % at the end of it has been selected as best formulation and subjected to stability study as per ICH guidelines. There was no significance change in properties of the optimized formulation and the drug release before and after stability studies.

Conclusion

The data obtained from the study of "Design, Development and Evaluation of Microemulgel containing Econazole nitrate'' reveals the following conclusions.

1. Econazole nitrate Microemulgel formulations were successfully prepared using different excipients.
2. The consistency, homogeneity was good of all microemulgel.
3. The pH of the prepared microemulgel was found to be range of the 5.7-6.8
4. In vitro percentage drug release of prepared Econazole nitrate Microemulgel were found to be in the range of 81.03-98.89%.
5. Stability of prepared microemulgel formulations were evaluated at periodical intervals of time for 3 months accelerated storage conditions. The average pH spreadability remained relatively unchanged with no significant change in vitro drug release after 3 months.

6. Hence the result of F9 formulation was found to be the best formulation study indicated promising potentials for delivering Econazole nitrate Microemulgel as topically in the treatment of fungal infection and could be viewed as a potential alternative to conventional dosage forms.

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