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Formulation Development & Evaluation of Econazole Nitrate Topical Emulgel

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Abstract

Topical drug delivery has been used for centuries for the treatment of local skin disorders. Emulgel have emerged as one of the most interesting topical delivery system as it has dual control release system i.e. gel and emulsion. One side the topical applications of the drug offers the potential advantages of delivering the drug directly to the site of action and secondly delivering the drug for extended period of time at the effected site. The major objective behind this formulation is enhancing the topical delivery of hydrophobic drug (Econazole Nitrate) by formulating Econazole nitrate Emulgel using three types of gelling agents: water soluble polymer Carbopol 934, Carbopol 940 and Hydroxypropyl methylcellulose (HPMCK4M). Oleic acid is used as permeation enhancer. The prepared Emulgel were evaluated for their physical appearance, pH determination, viscosity, spreadability, extrudability, in vitro drug release, skin irritation test and stability. All the prepared Emulgel formulation showed acceptable physical properties, consistency, spreadability, viscosity and Ph value. The best Optimized formulation F1 compared with marketed Econazole Nitrate xiii cream. The in vitro release rate of Emulgel was evaluated using Diffusion cell containing Rat skin membrane with phosphate buffer pH 7.4 as the receptor medium. The release rate of the optimized F1 Formulation was found to follow Higuchi model. The Emulgel were found to be stable with respect to colour, pH, and drug content at room temperature and conditions for one month.

Keywords: Emulgel, Econazole Nitrate, Carbopol, Spreadability, Extrudability.

1. Introduction

1.1 Physiology of the skin

The skin has several layers. The overlaying outer layer is called epidermis; the layer below epidermis is called dermis. They dermis contain a network of blood vessels, hair follicle, sweat gland & sebaceous gland. Beneath the dermis are subcutaneous fatty tissues. Bulbs of hair project in to these fatty tissues.

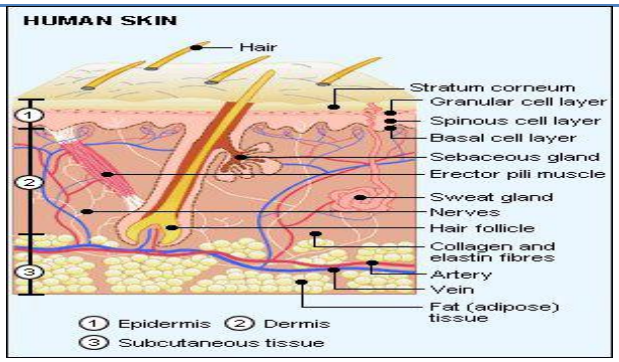

Figure 1: Structure of skin

The layers of epidermis are:

- ✓ Stratum Germinativum (Growing Layer)
- ✓ Malpighion Layer (pigment Layer)
- ✓ Stratum Spinosum (Prickly cell Layer)
- ✓ Stratum Granulosum (Granular Layer)
- ✓ Stratum Lucidum
- ✓ Stratum Corneum (Horny Layer)

Functions of Skin1

1) Containment of body fluids and tissues.
2) Protection from external stimuli like chemicals, light, heat, cold and radiation.
3) Reception of stimuli like pressure, heat, pain etc.
4) Biochemical synthesis.
5) Metabolism and disposal of biochemical wastes.
6) Regulation of body temperature.
7) Controlling of blood pressure.
8) Preventing penetration of noxious foreign material & radiation.
9) Cushioning against mechanical shock.
10) Interspecies identification and/ or sexual attraction.

1.2 Topical dosage forms [1-5]

The topical drug delivery system is generally used in pain management, contraception, and urinary incontinence. Topical formulation would be based on the facility to reach the target into the skin (biopharmaceutics) and the demonstration of the local therapeutic effect (pharmacology of the drug to the surface of the skin or within the skin).

Topical delivery includes two basic types of product:

External topical that are spread, sprayed, or otherwise dispersed on to cutaneous tissues to cover the affected area.

Internal topical that are applied to the mucous membrane orally, vaginally or on anorectal tissues for local activity.

Advantages of topical dosage forms [2,6]

- ✓ They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH and enzymatic activity and drug interaction with food and drinks.
- ✓ They can substitute for oral administration of medication when that route is unsuitable.
- ✓ To avoid the first pass effect, that is, the initial pass of drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzyme.
- ✓ They are non-invasive and have patient compliance.
- ✓ They are less greasy and can be easily removed from the skin.
- ✓ They are cost effective. They reduce doses as compare to oral dosage forms.
- ✓ Their effect is localized with minimum side effects.

Disadvantages of topical dosage forms [2,7]

- ✓ Drugs with reasonable partition coefficient and possessing solubility both in oil and water are most ideal, as drug must diffuse through lipophilic stratum corneum and hydrophilic viable epidermis to reach the systemic circulation.
- ✓ Only drugs, which are effectively absorbed by the percutaneous routes as such or by using penetration promoters, can be considered.
- ✓ The route is not suitable for drugs that irritate or sensitize the skin.
- ✓ The route is restricted by the surface area of delivery system and the dose that needs to be administered in the chronic state of disease.
- ✓ Topical drug delivery systems are relatively expensive compared to conventional dosage forms. They may contain a large amount of drug, of which only a small percentage may be used during the application period.

1.3 Emulgels[10,11]

When gels and emulsions are used in combined form the dosage forms are referred as emulgels. As the name suggest they are the combination of emulsion 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 gels by decreasing 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 emulsion into an emulgel.

Emulgels for dermatological use have several favourable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, bio-friendly and transparent with longer shelf life and pleasing appearance. Use of topical agents requires an appreciation of the factors that influence percutaneous absorption.

Advantages of Using Emulgels as a Drug Delivery System

1) Hydrophobic drugs can be easily incorporated: Most of the hydrophobic drugs cannot be incorporated directly into gel base because solubility act as a barrier and problem arises during the release of the drug. Emulgel helps in the incorporation of hydrophobic drugs into the oil phase and then oily globules are dispersed in aqueous phase resulting in o/w emulsion. And this emulsion can be mixed into gel base. This may be proving better stability and release of drug than simply incorporating drugs into gel base.

2) Better stability: Other transdermal preparations are comparatively less stable than emulgels. Like powders are hygroscopic, creams shows phase inversion or breaking and ointment shows rancidity due to oily base.

3) Better loading capacity: Other novel approaches like niosomes and liposomes are of nano size and due to vesicular structures may result in leakage and result in lesser entrapment efficiency. But gels due to vast network have comparatively better loading capacity.

4) Production feasibility and low preparation cost: Preparation of emulgels comprises of simpler and short steps which increases the feasibility of the production. There are no specialized instruments needed for the production of emulgels. Moreover materials used are easily available and cheaper. Hence, decreases the production cost of emulgels.

5) No intensive sonication: Production of vesicular molecules needs intensive sonication which may result in drug degradation and leakage. But this problem is not seen during the production of emulgels as no sonication is needed.

Important Constituents of Emulgel Preparation

1) Aqueous Materials
2) Oils
3) Emulsifiers
4) Gelling Agent
5) Permeation Enhancers
6) Co-surfactants
7) Preservative

2. Material & Methodology

2.1 Material

Econazole nitrate was a gift sample from FDC limited Mumbai, India. Carbopol 934, 940 was gifted by (Corel pharma chem. Ahmedabad (India)) and Propylene glycols, Oleic acid, Tween 20, Span 20, Tri ethanol amine were obtained from (Astron chemicals Ahmedabad (India)). HPMC K4M was gifted by (Yarrow Chem. product, Mumbai (India)). Methanol was gifted by (Merck Specialities private Limited). All other ingredients and reagents were of analytical grade.

2.2 Method

Different formulations were prepared using varying amount of gelling agent. The method only differed in process of making gel in different formulation. The preparation of emulsion was same in all the formulations. The gel bases were prepared by dispersing Carbopol 934 and Carbopol 940 in distilled water separately with constant stirring at a moderate speed using magnetic stirrer. Formulations F1, F2 and F3 were prepared by Carbopol 934 and F4, F5 and F6 by Carbopol 940 as gelling agent. In formulations F7, F8 and F9 the gel were prepare by dispersing HPMC K4M in heated distilled water (75°C) and the dispersion was cooled and left overnight. The pH of all the formulations was adjusted to 6 to 6.5 using tri ethanol amine (TEA).

The oil phase of the emulsion was prepared by dissolving Span 20, econazole nitrate in oleic acid, while the aqueous phase was prepared by dissolving Tween 20 in purified water. Methyl paraben, propyl paraben and remaining small quantity econazole nitrate in propylene glycol. Both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70° to 80°C, then the oily phase was added to the aqueous phase with continuous stirring until it got cooled to room temperature. The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the Emulgel

2.3 Evaluation of Emulgel

2.3.1 Physicochemical Characteristics of Econazole Nitrate Emulgel Formulations

pH [12, 51]

The pH of Emulgel formulations was determined by using digital pH meter. One gram of emulgel was dissolved in 100 ml of distilled water and it was placed for two hours. The measurement of pH b y calibrated digital pH meter. (Labtronics model LT 11 pH meter)

Viscosity [12, 51]

The viscosity of the formulated batches was determined using a Brookfield Viscometer (Brookfield DV-2 + pro) with spindle S61. 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 12 rpm for 10 minutes. The viscosity reading was noted down.

Drug Content [12, 51]

Weigh accurately 1 gm of Emulgel in volumetric flask and it was dissolved in 30 ml of Methanol and volume was made up to 100 ml using phosphate buffer pH 7.4. The volumetric flask was kept for 2 hours and shaken well in a shaker to mix it properly. The solution was passed through the filter paper and filtered. The absorbance was measured UV- spectrophotometer at 271nm. The drug content was determined using following formula

Drug content =
(concentration * Dilution factor * volume taken) * Conversion factor

Spreadability Test[12,51]

Spreadability is determined by apparatus suggested by Mutimer et al which is suitably modified in the laboratory and used for the study. It consists of a wooden block, which is provided by a pulley at one end. By this method, spreadability is measured on the basis of 'Slip' and 'Drag' characteristics of emulgels. A ground glass slide is fixed on this block. An excess of emulgel (about 3 gm) under study is placed on this ground slide. The emulgel is

then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. A 1 Kg weight is placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the emulgel between the slides. Excess of the emulgel is scrapped off from the edges. The top plate is then subjected to pull of 70 gms. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted. A shorter interval indicates better spreadability is calculated by using the formula:

S = M*L / T

Where M = weight tied to upper slide
L = length of glass slides
T = time taken to separate the slides

Extrudability Test (Tube Test)[12, 51]

Extrudability test is based upon the determination of weight required to extrude 0.5 cm ribbon of Emulgel in 10 sec from lacquered collapsible aluminum tube. The extrudability was then calculated by using the following formula.

Extrudability =
weight applied to extrude emulgel form tube (in gm)/ area (in cm2)

2.3.2 *In Vitro* Drug Release [12, 38, 51]

The *in vitro* drug release studies prepared formulations and marketed formulation Ecodex cream 1 % (J. B. chemical and pharmaceutical limited) were studied of the Emulgel were carried out in modified Diffusion cell using rat skin. The rat skin was soaked in phosphate buffer pH 7.4 for 9-12 h. the rat skin clamped carefully to one end of the hollow glass tube of dialysis cell (2.3 cm diameter; 4-16 cm2 area). Then Emulgel was spread uniformly on the rat skin. 50 ml of phosphate buffer was taken in a beaker, which was used as receptor compartment. The donor compartment was kept in contact with receptor compartment. This whole assembly was kept on a magnetic stirrer and the solution on the receptor side was stirred continuously using a magnetic bead and temperature of the cell was maintained at 37°±0.5ºC. A similar blank set was run simultaneously as a control. Sample (10 ml) was withdrawn at suitable time intervals and replaced with equal amounts of fresh dissolution media. The Samples were analyzed UV spectrophotometer at 271nm and the cumulative percent drug release was calculated.

Kinetic study and Mechanism of drug release [52-58]

To find out the release mechanism of drug from emulgel, release study data were subjected to statistical analysis by Zero order, First order, Higuchi and Korsmeyer Peppas equations.

Data obtained from in-vitro drug release studies were fitted to following kinetic models.

1. Zero order release kinetics: In many of the modified release dosage forms, particularly sustained or controlled release dosage forms, is zero-order kinetic.

Q=K0t…… (1)

Where Q is fraction of drug released at time t & K0 is zero order release rate constant.

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K_0.

2. First order release kinetics: The drug release from most of the slow release tablets could be described adequately by apparent first order kinetics.

The equation that describes first order kinetics is

In (1-Q) = -K1t …… (2)

Where Q is the fraction of drug released at time t. And K1 is the first order release rate Constant.

Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

3. Higuchi Model: It defines a linear dependence of the active fraction released per unit of surface (Q) on the surface root of time. The dissolution pattern of the drug is dictated by water penetration rate (diffusion controlled) and thus the following relationship applies:

Q = K2 t1/2…… (3)

Where, K2 is release rate constant.

A plot of the fraction of drug released against root of time will the linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Flick's Law.

4. Peppas & Korsemeyer Model (Power law): In order to define a model, which would represent a better fit for the formulation dissolution data was further analyzed by Peppas & Korsemeyer equation,

Mt \ Mα = Kt n……(4)

Where, Mt is the amount of drug released at time t and M á is the amount released at Time α, thus the Mt \ Mα is the fraction of drug released at time t, K is the kinetic constant and n is the diffusional exponent. To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted. A plot between log of Mt \Mα against log of time will be linear if the release obeys Peppas & Korsemeyer equation and the slope of this plot represents n value.

The value of n indicates the drug release mechanism. For a slab the value $n \leq 0.45$ indicates Fickian diffusion, values of $n > 0.45$ and ≤ 1.0 indicate non-Fickian mechanism.

2.3.3 Optimized batch F1 evaluation

Optimized batch F1 compare with *In Vitro* Drug Release, pH, Drug content, Spreadability marketed formulation Ecodex cream 1 % (J. B. chemical and pharmaceutical limited)

Globule Size and Zeta Potential of Optimized batch F1

Globule Size and Zeta Potential of emulsions were determined by Zetatrac. Zetatrac determines Zeta Potential by measuring the response of charged particles to an electric field. In a constant electric field particles drift at a constant velocity. Through the velocity, the charge and Zeta Potential are determined. Zetatrac utilizes a high frequency AC electric field to oscillate the charged particles. The Brownian motion power spectrum is analyzed with the Nanotrac controlled reference technique of particle sizing to determine the Modulated Power Spectrum, a component of the power spectrum resulting from the oscillating particles. Zeta Potential is calculated from the MPS signal. Also determined are the particle mobility (velocity per electric field), particle charge and particle size.

A 1.0 gm sample was dissolved in purified water and agitated to get homogeneous dispersion. Sample was injected to photocell of zetatrac. globule size and zeta potential was obtained.

2.3.4 Skin irritation Test optimised Batch F1[34, 37]

All the experimental procedures were carried out in accordance with committee for purpose of experiments on animal's guidelines (CPSCEA). The study was reviewed and approved by Institutional Ethics Committee (Protocol number: SDPC/14/2013), Shree Dhanvantary Pharmacy College, India. OECD Guideline 404 Acute Dermal Irritation followed A 3 gm sample of the test group (Optimized batch F1 econazole nitrate emulgel) and Standard group (Ecodex cream 1 %)was then applied to each site (two sites per Guinea pig) by introduction under a double gauze layer to an area of skin approximately 1" x 1"(2.54 x 2.54 cm) square. The sample re-applied on the skin of Guinea pig. Animals were returned to their cages. After a 24 hour exposure, the samples are removed. The test sites were wiped with tap water to remove any remaining test group and Standard group sample residue.

2.3.5 Stability Study of Optimized batch F1

Stability study of selected optimized batch F1 was done at room temperature (40oC± 2oC / 75 % RH ± 5%) for 1 month and formulation was finally evaluated for colour, drug content and pH.

3. Result & Discussion

3.1 Fourier Transfer Infrared Spectroscopy (FT-IR)

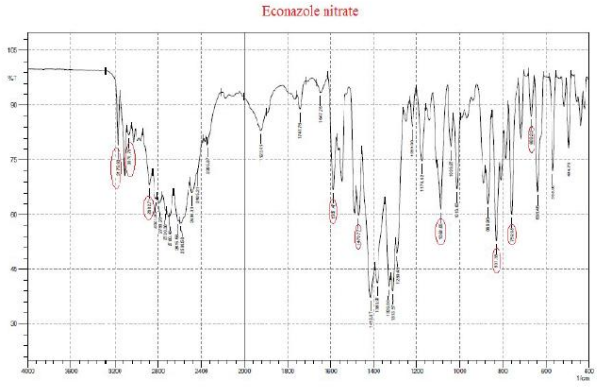

Figure 2: Fourier Transfer Infrared Spectroscopy (FT-IR)

IR spectrum shows all functional characteristic peaks of econazole nitrate as given in Figure.

3.2 Melting Point

Melting point of econazole nitrate was found to be 162-166˚C which was identical to the official standard (165˚C).

3.3 Screening of Excipients

To find out suitable excipients, the solubility study of econazole nitrate was performed. Solubility in various excipients is shown in table.

Table 1: Solubility Study Data

Components	Solubility (mg/ml)
Water	0.17 mg/ml
Linseed oil	14.71 mg/ml
Castor oil	19.24 mg/ml
Campul 908P	21.19 mg/ml
Oleic acid	**39.16 mg/ml**
Phosphate buffer 7.4	0.71mg/ml
Propylene glycol	**37.98 mg/ml**
Tween 80	15.12 mg/ml
Span 80	4.3 mg/ml
Tween 20	**16.7 mg/ml**
Span 20	**8.6 mg/ml**
PEG 200	35.13 mg/ml
PEG 400	32.41 mg/ml

From data shown in Table, highest solubility of econazole nitrate was found in Oleic acid oil, Tween 20, span 20 amongst surfactants and propylene glycol amongst co-surfactants. Hence these components were selected for preparation of emulgel system.

3.4 pH

Table 2: pH

Batch	pH
F1	6.3
F2	6.5
F3	6.4
F4	6.2
F5	6.1
F6	6.5
F7	6.2
F8	6.0
F9	6.4

pH values of all prepared formulation ranged from 6.0 to 6.5

3.5 Viscosity

Table 3: Viscosity (Spindle S61 at 12 RPM)

Batch	Viscosity (CPS)
F1 (carbopol 934 1%)	8377.15
F2 (carbopol 934 1.2%)	9770.92
F3 (carbopol 934 1.4%)	14341.41
F4 (carbopol 934 1%)	12045.27
F5 (carbopol 934 1.2%)	15942.31
F6 (carbopol 934 1.4%)	17842.55
F7 (HPMC k4M 1%)	3241.78
F8 (HPMC k4M 1.2%)	4341.02
F9 (HPMC k4M 1.4%)	6033.15

From data shown in Table, The viscosity of the formulations increases as concentration of polymer increases.

3.6 Drug Content

Table 4: Drug Content

Formulation Drug content	Formulation Drug content
F1 (carbopol 934 1%)	91.42 %
F2 (carbopol 934 1.2%)	88.29 %
F3 (carbopol 934 1.4%)	85.48 %
F4 (carbopol 934 1%)	82.65 %
F5 (carbopol 934 1.2%)	89.72 %
F6 (carbopol 934 1.4%)	87.37 %
F7 (HPMC k4M 1%)	86.41 %
F8 (HPMC k4M 1.2%)	81.17 %
F9 (HPMC k4M 1.4%)	87.42 %

From data shown in Table, The drug content of the formulated Emulgel was estimated Shimadzu 2450 UV-visible double beam spectrophotometer at λmax 271 nm, highest drug content found optimize formulation F1 91.42 %

3.7 Spreadability Test

Table 5: Spreadability Test

Formulation	Spreadability Test (gm*cm/sec)
F1 (carbopol 934 1%)	29.16
F2 (carbopol 934 1.2%)	27.65
F3 (carbopol 934 1.4%)	22.82
F4 (carbopol 934 1%)	30.88
F5 (carbopol 934 1.2%)	26.25
F6 (carbopol 934 1.4%)	22.82
F7 (HPMC k4M 1%)	32.81
F8 (HPMC k4M 1.2%)	29.16
F9 (HPMC k4M 1.4%)	23.86

From data shown in Table 5.9 the spreadability indicates that the Emulgel is easily spreadable by small amount of shear. Spreadability of the Emulgel decreases with the increase in the concentration of the polymer.

3.8 Extrudability Test (Tube Test)

Table 6: Extrudability Test (Tube Test)

Formulation	Extrudability test (gm/cm^2)
F1 (carbopol 934 1%)	16
F2 (carbopol 934 1.2%)	22
F3 (carbopol 934 1.4%)	26
F4 (carbopol 934 1%)	18
F5 (carbopol 934 1.2%)	22
F6 (carbopol 934 1.4%)	30
F7 (HPMC k4M 1%)	04
F8 (HPMC k4M 1.2%)	12
F9 (HPMC k4M 1.4%)	14

From data shown in Table, Extrudability test of the formulations increase as concentration of polymer increases.

3.9 *In Vitro* Drug Release

Table 7: *In Vitro* Drug Release

Time (Hr.)	% Cumulative Drug Release									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	Marketed formulation Ecodex cream 1%
0	0	0	0	0	0	0	0	0	0	0
1	22.33	21.33	19	8.66	10.33	7.66	7.33	6.66	5.66	6.17
2	31.78	30.73	28.61	17.43	15.85	15.71	12.36	11.66	11.95	13.09
3	39.69	38.61	36.1	25.21	25.41	23.44	19.98	19.26	16.6	18.41
4	46.46	44.68	42.05	36.25	37.88	36.03	27.49	24.11	24.27	27.56
5	54.79	53.25	51.16	45.48	42.93	41.02	36.96	32.11	33.28	32.03
6	60.81	59.53	56.71	50.82	49.79	47.77	44.88	41.44	40.04	43.70
7	65.37	64.69	62.41	57.31	55.25	53.15	52.13	50.5	47.4	49.91
8	71.01	69	66.64	66.31	62.51	60.33	59.31	55.34	52.75	57.47
9	77.12	74.38	70.95	72.03	69.36	66.11	65.09	63.58	58.91	61.42

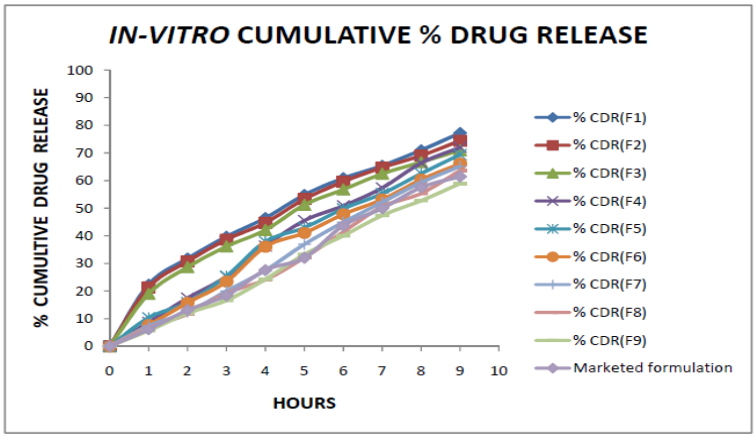

Figure 3: Comparative *In Vitro* Drug Release Profiles of Formulations F1-F9 and Marketed Formulation

From data shown in Table, It has been concluded that, if we increase the concentration of polymer, the diffusion of drug through the membrane (rat skin) also decreases. Highest diffusion of drug found optimize formulation F1 77.12 % at 9 hr. and marketed formulation diffusion of drug 61.42 % at 9 hr.

3.9 Kinetic Study and Mechanism of Drug Release

The correlation coefficient value (R^2) of each formulation for zero order, first order, Higuchi and Korsmeyer-Peppas model are shown in table.

Table 8: Kinetics and Release Mechanism of Optimized Batch F1

Batch	R^2 Value				
	Zero Order	First Order	Higuchi	Korsemeyer- Peppas	
	R^2	R^2	R^2	R^2	n
F1	0.951	0.991	0.994	0.603	0.49

4. Conclusion

In the present work Econazole Nitrate Emulgel Prepared Using Different Polymers in Different concentration. From the above results we can conclude that Econazole nitrate Emulgel formulations prepared with either Carbopol 934, Carbopol 940, HPMC K4M showed acceptable physical properties, *In-vitro* drug release studies through rat skin, Drug content, Spreadability test, Viscosity, Extrudability test, and pH. However, the Carbopol 934 based Emulgel in its low concentration with the formulation code F1 proved to be the formula of choice, since it showed the highest drug release.

The optimized F1 batch was selected for 1 month stability study, there was no significant change in colour, pH and % drug content which indicated the selected formulation is stable.

The optimized formulation F1 (emulgel) show better Spreadability test, *In-vitro* drug release profile than marketed preparation. So, Econazole nitrate optimized emulgel formulation can be used to treat the topical fungal diseases.

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