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Formulation and Evaluation of Tioconazole Emulgel for Topical Drug Delivery System

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ABSTRACT

The aim of present work was to develop a emulgel for the topical delivery system which is useful in the treatment of vaginal fungal infection. Emulgels having advantage of both emulsion & gels which act as a controlled drug delivery system for topically applied drugs. The Gel in formulations were prepared by dispersing Carbopol 934 & Carbapole 940 in purified water. Then oil phase & aqueous phase of the emulsion were prepared. Both the oily and aqueous phases were heated separately & then oily phase were added to the aqueous phase. add Glutaraldehyde in during of mixing of gel and emulsion in ratio 1:1 to obtain the emulgel. Prepared emulgels was investigated for different parameters. All the prepared emulgels showed acceptable physical properties concerning colour, viscosity, melting point, pH value, and spreadability. The results of *in-vitro* drug release showed that carbopol 934 was the formula of choice as it showed better drug release & antifungal activity. FTIR studies revealed that drug and all excipients are compatible. The data obtained from *in- vitro* permeation studies was treated by various conventional mathematical models (zero order, first order, Higuchi and Korsmeyer- peppa's) to determine the release mechanism from the designed emulgel formulations. Selection of a suitable release model was based on the values of R^2 (correlation coefficient), k (release constant) obtained from the curve fitting of release data. It was found that all the formulations follows the first order kinetics. The regression coefficients for the all formulations F1 to F4 of Higuchi plot was found to be almost linear.

Key words: Emulgel, tioconazole, antifungal drug, topical drug delivery.

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INTRODUCTION

Topical drug delivery is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal & skin as topical routes. These are apply a wide range of preparations for both cosmetic and dermatological to their healthy or diseased skin[1]. Emulgels with advantage of both gels & emulsion act as a controlled drug delivery system for topically applied drugs. They are emulsion of either oil in water type or water in oil type which are gelled by mixing with a gelling agent. Gels have extends the contact period of medication over the skin due to mucoadhessive property. Both water-in-oil & oil-in-water type of emulsion are used in topical preparation as water washable preparation & emollients for dry skin respectively. The penetration process becomes easy if the emulsion in nature becomes less thixotropic i.e. less viscous on shearing. In a order to increase emulsion ability & stability to penetrate stratum corneum it is jellified in a gel base & the resulting preparation is called Emulgels. Gels in dermatological preparation have advantage of ease of application & offer better stability as compare to cream & ointements[2]. From the BCS classification of the four classes drugs class II drugs show poor solubility & high permeability. It is clear that for class II drugs having low ability to dissolve is a more significant drawback to their whole rate & amount of absorption then their ability to permeate through the membrane. Hence, when one is concerned with topical delivery of poorly water-soluble drug Emulgels may serve as better choice. For hydrophobic or poorly water-soluble drugs emulsified gel has proven a stable one and better vehicle.

Disease profile

Fungal infection like Candidiasis is due to any type of *Candida* (a type of yeast). When it affects the vagina, it is commonly called a yeast infection. Severe itching, burning, soreness, irritation, and a whitish or whitish-gray cottage cheese-like discharge is caused by infection of the vagina or vulva. These symptoms are also present in the more common bacterial vaginosis. In a 2002 study, only 33% of women who were self-treating for yeast infection actually had such an infection, while many had either bacterial vaginosis or a mixed-type infection. Symptoms of infection of the male genitalia (balanitis thrush) include red skin around the head of the penis, irritation, swelling, itchiness and soreness of the head of the penis, thick, lumpy discharge under the foreskin, unpleasant odour, and pain when passing urine or during sex and odour, difficulty retracting the foreskin (phimosis).

Diagnosis of infection of yeast is done either via microscopic examination or culturing. For identification by light microscopy, a scraping or swab of the affected area is placed on

a microscope slide. A single drop of 10% potassium hydroxide (KOH) solution is then added to the specimen.

For the method of culturing, a sterile swab is rubbed on the infected skin surface. The swab is then streaked on a culture medium. The culture is incubated at 37 °C for several days, to allow development of bacterial or yeast colonies. The characteristics (such as colour and morphology) of the colonies may allow initial diagnosis of the organism causing disease symptoms.

A diet that supports the immune system and is not high in simple carbohydrates contributes to a healthy balance of the oral and intestinal flora. While yeast infections are associated with diabetes, the level of blood sugar control may not affect the risk. Wearing cotton underwear may help to reduce the risk of developing skin and vaginal yeast infections, along with not wearing wet clothes for long periods of time.

For women who had experience recurrent yeast infections, there is limited evidence that oral or intravaginal probiotics help to prevent future infections. This includes either as yogurt or as pills.

MATERIALS AND METHODS

Tioconazole was obtained as a gift sample from Themis medicare Pvt. Ltd. Haridwar, India. Carbapole 940, carbapole 934, methyl paraben , propyl paraben, glutaraldehyde was purchased from Central drug house Pvt. Ltd. Delhi (IND).

Preformulation studies:

Preformulation testing is the first step in the rationale development of dosage form to a drug. It can be defined as the investigation of physical and chemical properties if drug substance alone or in combination with excipients. The overall objectives of preformulation studies is to generate information useful in formulaton of developing stable and bioavailable dosage form which can be mass produced.

Identification tests

Identification of drug by through Fourier transform infrared (F.T.I.R.)

Infrared spectrum of tioconazole was determined by using Fourier Transform Infrared Spectrophotometer using KBr disks method. The sample (0.5 to 1.0 mg) is finely grounded and intimately mixed with approximately 100 mg of dry potassium bromide powder. Grinding and mixing can be done with mortar and pestle. The mixture is then pressed into a transparent disk in an evacuable die at sufficiently high pressure. Suitable KBr disks or pellets can often be made using a simpler device such as a hydraulic press. The base line correction was done using dried potassium bromide. Then, the spectrum of dried mixture of drug and potassium bromide was

scanned from 2000 cm^{-1} to 400 cm^{-1} compare with reference graph. FTIR has been used to assess the interaction between drug and polymers.

Physical appearance[3]:

The prepared emulsion preparations were examined visually for their color, homogeneity, consistency & pH.

Spreadability:

Spreadability is determined by apparatus recommended by Mutimer et al (1956) which is appropriately modified in the laboratory & 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' & 'Drag' characteristics of emulgels. A ground glass slide is fixed on this block. On this ground slide an excess of emulgel (about 2gm) under study is placed. The emulgel is then sandwiched between this slide & another glass slide having the dimension of fixed ground slide & provided with the hook. A 1 kg weight is placed On the top of the two slides for 5 minutes to expel air & 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 80gm. With the help of string attached to the hook & the time (in seconds) necessary for the top slide to cover a distance of 7.5cm be noted. Better spreadabilityis indicate by lesser time[4]. Spreadability was calculated by using the formula,

$$S = ML/T$$

Where, S = Spreadability,

M = Weight tied to upper slide,

L = Length of glass slide;

T = Time taken to separate the slides completely from each other.

Rheological Studies:

The viscosity of the different emulgel formulations is determined at 25°C using a cone & plate viscometer with spindle 52 (Brookfield Engineering Laboratories,) & attached to a thermostatically controlled circulating water bath[5].

Drug Content Determination[6]:

1gm of emulgel is mixed with appropriate solvent. Then filter it to get clear solution. Using UV spectrophotometer determine its absorbance. Standard plot of drug is prepared in the same solvent. Concentration & drug content can be determined by using the same standard plot by putting the value of absorbance in the standard plot equation:

Drug Content = (Concentration × Dilution Factor × Volume taken) × Conversion Factor.

Skin Irritation Test (Patch Test):

The preparation is applied on the properly shaven skin of rat & its adverse effect like change in color, change in skin morphology should be checked up to 24 hours. The total set of 8 rats can be used for the study. Test is passed if no irritation occurs. If the skin irritation symptom arises in more than 2 rats the study should be repeated[7].

***In-Vitro* Release/Permeation Studies**:

Using Franz diffusion cell *In-vitro* release studies were carried out.

Drug release kinetic study[8]

The mechanism of drug release from the topical gel is analyzed by fitting the release data to following equations

Zero – order equation:

$$Q = k_0 t$$

Where, Q is the amount of drug released at time t

k_0 is the zero – order release rate.

First – order equation:

$$\text{In } (100 - Q) = \text{In } 100 - k_1 t$$

Where, Q is the percent of drug release at time t

k_1 is the first – order release rate constant.

Higuchi's equation:

$$Q = k_2 \sqrt{t}$$

Where, Q is the percent of drug release at time t

k_2 is the diffusion rate constant.

Microbiological assay:

Agar well method & disc diffusion method were used to calculate percentage inhibition & zone of inhibition activity of emulgel formulation respectively. These techniques are used for evaluation of bacteriostatic or fungistatic activity of compound. It is mainly applied for semi solid formulations. Sabouraud's agar plates were prepared and dried. Then agar well was made by using cork boarer and the microbial strain was streaked on the plate while on other Sabourauds plate the strain was spread. Now 0.25 gm of emulgel is placed in agar well cut in the plate and disk prepared from whattman filter paper and sterilized was dipped in the emulgel formulation and placed on the plates with spread culture strain of fungus. After incubation for 24-48 hrs at 25^{o}C the plates were observed for inhibition of growth of fungus and zone of inhibition was measured in mm and

percent inhibition was measured as follows:

$$\% \text{ inhibition} = L_2 / L_1 \times 100$$

Where, L_1 = total length of the streaked culture,

L_2 = length of inhibition[9].

Stability Studies:

Stability study was performed on F_1 and F_3 formulations. The preparation was kept in glass container (5gm) and subjected to stability studies at room temp. & 4ºc temp for a period of three months. Sample were withdrawn at interval of 45 days and were evaluated for pH viscosity and drug content[8].

Method of preparation of Emulgel:

The Gel in formulations were prepared by dispersing Carbopol 934 in purified water with constant stirring at a moderate speed and Carbopol 940 in purified water with constant stirring at a moderate speed then the pH are adjusted to 6 to 6.5 using Tri Ethanol Amine (TEA). The oil phase of the emulsion were prepared by dissolving Span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in purified water**.** Methyl and Propyl paraben was dissolved in propylene glycol whereas drug (Tioconazole) was dissolved in ethanol and both solutions was mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70° to 80°C; then the oily phase were added to the aqueous phase with continuous stirring until cooled to room temperature. And add Glutaraldehyde in during of mixing of gel and emulsion in ratio 1:1 to obtain the emulgel.

Composition of emulgel formulation

Table No. 1: Composition of emulgel

S.No.	Ingradients (%w/w)	F1	F2	F3	F4
1	Tioconazole	0.1	0.1	0.1	0.1
2	Carbopol 940	0.5	0.5	-	-
3	Carbopol 934	-	-	0.25	0.25
4	Glutaraldehyde	0.05	0.05	0.05	0.05
5	Span 20	0.45	0.45	0.75	0.75
6	Tween 20	0.3	0.3	0.5	0.5
7	Light liquid paraffin	2.5	2.5	3.75	3.75
8	Methyl paraben	0.01	0.01	0.01	0.01
9	Propyl paraben	0.005	0.005	0.005	0.005
10	Purified water (q.s.)	50	50	50	50

RESULT & DISCUSSION

Four formulation of tioconazole were formulated using different drug polymer ratio. The formulation is subjected to evaluation parameter like viscosity, spreadability, drug content, *in-vitro*

drug release etc.

Preformulation studies:

Organoleptic properties of drug:

The color, odor and taste of the drug were characterized and recorded using descriptive terminology; the results are shown in Table No.2

Table No. 2: Results of Organoleptic properties

S.NO.	PROPERTIES	RESULT
1	Color	White to off white
2	Taste	Tasteless
3	Odor	Odorless
4	Appearance	Whitish Powder

Solubility of drug:

The solubility of the drug were checked in different solvents. This might be helpful in selection of a suitable solvent to dissolve drug as well as excipients used in formulations. Solubilty of drug depends on pH, ionic strength, temperature, buffer concentration. Tioconazole is soluble in chloroform & ethyl acetate, very slightly soluble in water, very soluble in ethanol and methanol.

Melting point:

The melting point of tioconazole was found to be 165-172ºC by capillary method. And after performing the experiment it was observed that the experimental melting point value is same as that of the literature citation of 168-170ºC.

Partition Coefficient:

The partition coefficient of tioconazole was calculated from the ratio between the concentration of tioconazole in organic and aqueous phase using following:-

$$P\ o/w = (C_{oil}/C_{aqueous})\ equilibrium$$

The partition coefficient of drug was found to be 6.77.

FTIR of standard tioconazole by British pharmacopoeia 2010

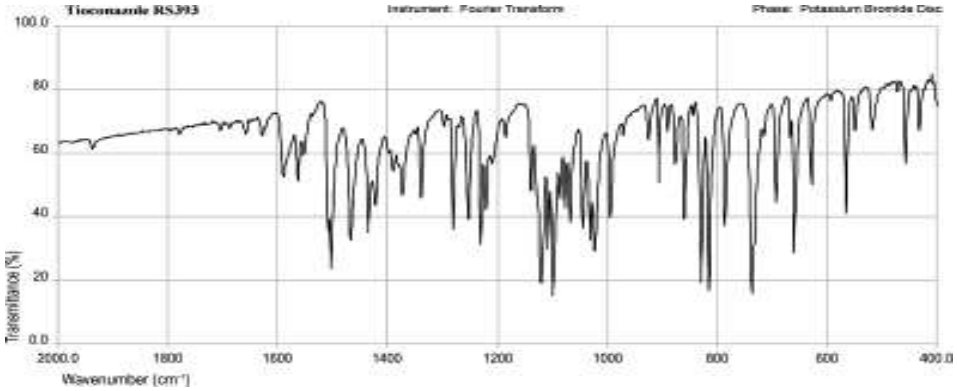


Figure 1: FTIR Spectrum of Tioconazole (with reference B.P. 2010).

Identification of sample tioconazole through FTIR

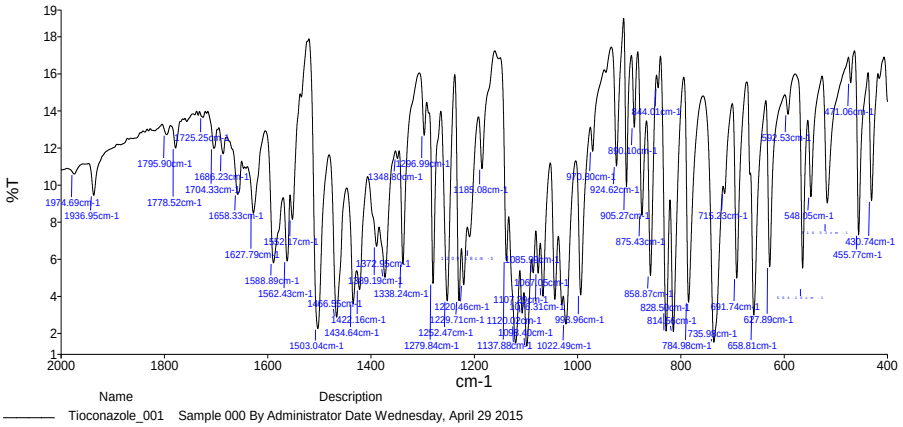


Figure 2: FTIR spectrum of sample tioconazole

The comparison between the peaks of two graphs shows that the characteristics peaks of tioconazole (taken from B.P.) was found to be similar to the given drug sample, which shows that the drug is tioconazole.

Spectral Studies

Drug- excipient Compatibility study:

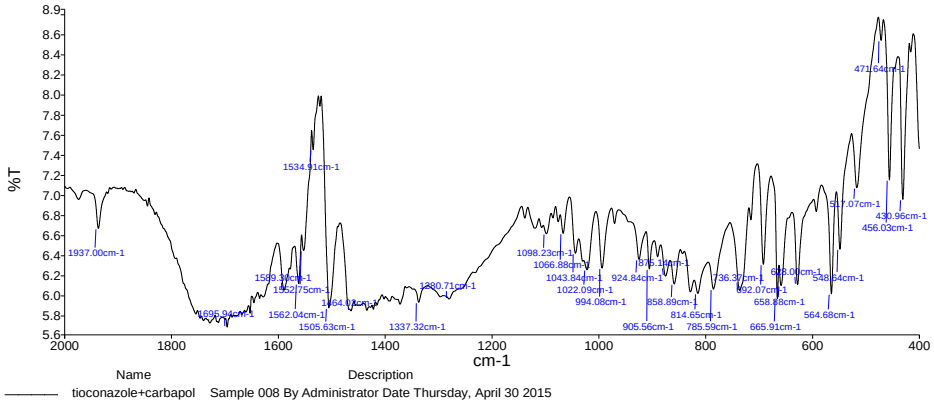


Figure 3: FTIR spectra of tioconazole + carbapol 934

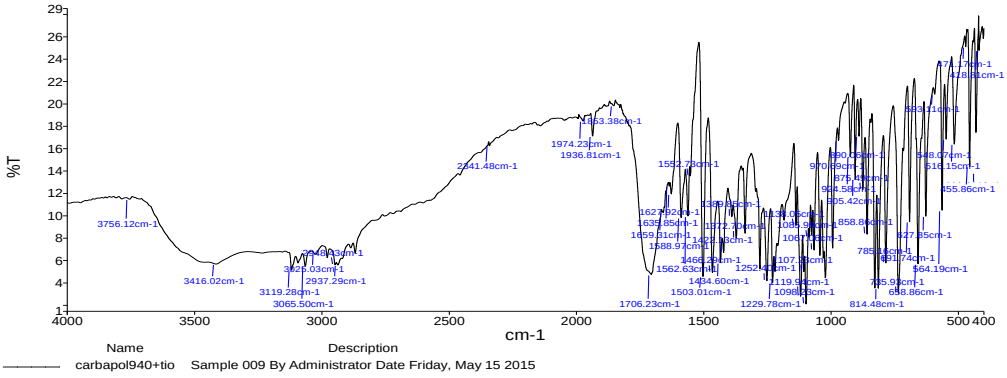


Figure 4: FTIR spectra of Tioconazole+ carbapol 940

The drug-polymer interactions shows that there was no major shifts in the absorption bands(peaks) in presence of polymer and it was observed that all the characteristics peaks of drug is present in the combination of drug and polymer spectra indicating the compatibility of drug with the polymer used.

Measurement of pH:

The pH of emulgel formulation was in the range of 5.9 to 6.8, which lies in the normal pH range of the skin & would not produce any skin irritation. There was no significant change in pH values as a function of time for all formulation.

Table No. 3: pH of emulgel formulation (mean±S.D., n=3)

Formulation	F_1	F_2	F_3	F_4
pH	5.91±0.1	6.63±0.05	6.67±0.17	6.81±0.57

Spreading Coefficient:

Spreading test was carried out for all the formulations. The spreadibilty indicates that the emulgel is easily spreadable by small amount of shear. The spreadibility is very much important as it shows the behavior of emulgel when it comes out from the tube. Spreadability of emulgel formulation lie between 13.32-17.41.

Table No. 4: Spreadibility of emulgel formulation (mean±S.D., n=3)

Formulation	F_1	F_2	F_3	F_4
Spreadibility (cm)	13.32±1.58	17.41±1.43	15±0.75	15.78±0.15

Rheological study:

Viscosity of formulation lie in the range of 2370-4200cps. Viscosity has profound significance with respect to the performance of topical products. Product characteristics, such as spreadability, ease of application, drug release and stability are closely linked to the viscosity of the formulation.

Table No. 5: Viscosity of emulgel formulation (mean±S.D., n=3)

S. No.	Formualtion	Viscosity
1.	F_1	2363
2.	F_2	2400
3.	F_3	4200
4.	F_4	4029

Drug content:

The drug content of the formulated emulgel was estimated spectrophotometrically at λ_{max}255 nm. All emulgel formulation showed the value of % drug content above 90%.

Table No. 6: Drug content of emulgel formulation (mean±S.D., n=3)

S. No.	Formualtion	Drug content
1.	F_1	93.45±0.41
2.	F_2	96.75±0.3

3.	F_3	97.66±0.57
4.	F_4	99.23±0.25

Microbiological assay:

The microbial activity of two formulated tioconazole emulgel i.e. F1 and F2 was performed. Percentage inhibition and zone of inhibition was taken as major of the drug anti microbial activity. It was observed that formulation F_1 and F_2 shows zone of inhibition of 68.70% & 48.31 respectively. F_1 and F_2 shows maximum zone of inhibition of 23 mm & 22 mm respectively.

***In-vitro* release study:**

The release of emulgel varied according to change in polymers. The release of drug from emulsified gel formulation can be ranked in following order; $F_{1>}$ $F_{2>}$ $F_{3>}$ F_4 where the amount of drug released after 8 hrs were 48.54%, 52.67%, 55.12% &59.97% respectively.

Table No. 7: *In-vitro* permeation profile of tioconazole formulation

S.No.	Time(hrs)	Cumulative % drug release			
		F1	F2	F3	F4
1.	0	0	0	0	0
2.	1	16.48	18.27	21.05	23.58
3.	2	25.13	26.83	28.49	30.22
4.	3	29.68	31.74	32.14	34.04
5.	4	32.51	34.57	35.91	37.19
6.	5	35.72	37.83	38.61	40.26
7.	6	43.91	45.77	46.16	48.64
8.	7	46.86	48.53	49.92	51.38
9.	8	48.54	52.67	55.12	59.97

Table No. 8: *In- vitro* permeation profile of Tioconazole from Formulation F1

S.No.	Time (hrs)	$\sqrt{T}$	Log T	% Cumulative drug release	% Cumulative drug remain	Log % Cumulative drug release	Log % Cumulative drug remain
1.	0	0	-	0	100	-	2
2.	1	1	0	16.48	83.52	1.21	1.92
3.	2	1.414	0.3	25.13	74.87	1.40	1.87
4.	3	1.732	0.47	29.68	70.32	1.47	1.84
5.	4	2	0.6	32.51	67.49	1.51	1.82
6.	5	2.236	0.69	35.72	64.28	1.55	1.80
7.	6	2.449	0.77	43.91	56.07	1.64	1.74
8.	7	2.645	0.84	46.86	53.14	1.67	1.72
9.	8	2.828	0.9	48.54	51.46	1.68	1.71

Table No. 9: *In- vitro* permeation profile of Tioconazole from Formulation F2

S.No.	Time (hrs)	$\sqrt{T}$	Log T	% Cumulative drug release	% Cumulative drug remain	Log % Cumulative drug release	Log % Cumulative drug remain
1.	0	0	-	0	100	-	2
2.	1	1	0	18.27	81.73	1.26	1.91

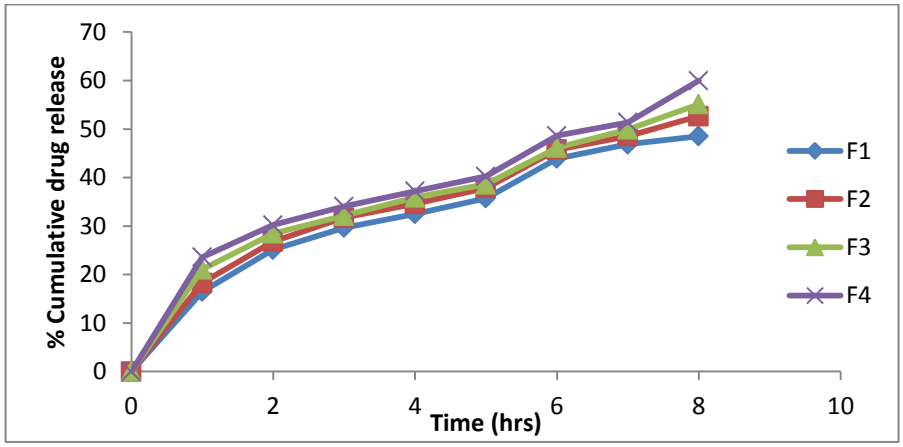
3.	2	1.414	0.3	26.83	73.27	1.42	1.86
4.	3	1.732	0.47	31.74	68.26	1.50	1.83
5.	4	2	0.6	34.57	65.43	1.53	1.81
6.	5	2.236	0.69	37.83	62.17	1.57	1.79
7.	6	2.449	0.77	45.77	54.23	1.66	1.73
8.	7	2.645	0.84	48.53	51.47	1.68	1.71
9.	8	2.828	0.9	52.67	47.33	1.72	1.67

Table No. 10: *In- vitro* permeation profile of Tioconazole from Formulation F3

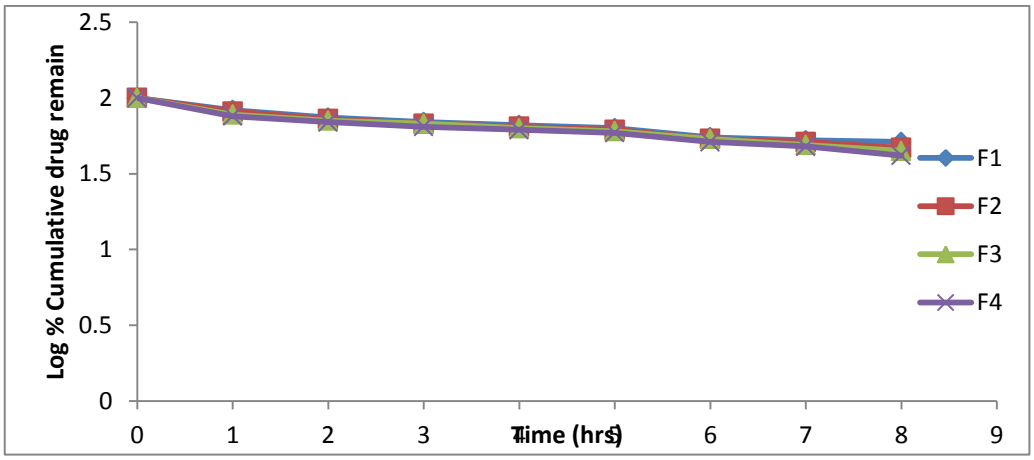
S.No.	Time (hrs)	$\sqrt{T}$	Log T	% Cumulative drug release	% Cumulative drug remain	Log % Cumulative drug release	Log % Cumulative drug remain
1.	0	0	-	0	100	-	2
2.	1	1	0	21.05	78.95	1.32	1.89
3.	2	1.414	0.3	28.49	71.51	1.45	1.85
4.	3	1.732	0.47	32.14	67.86	1.50	1.83
5.	4	2	0.6	35.91	64.09	1.55	1.80
6.	5	2.236	0.69	38.63	61.37	1.58	1.78
7.	6	2.449	0.77	46.16	53.84	1.66	1.73
8.	7	2.645	0.84	49.92	50.08	1.69	1.69
9.	8	2.828	0.9	55.12	44.88	1.74	1.65

Table No. 11: *In- vitro* permeation profile of Tioconazole from Formulation F4

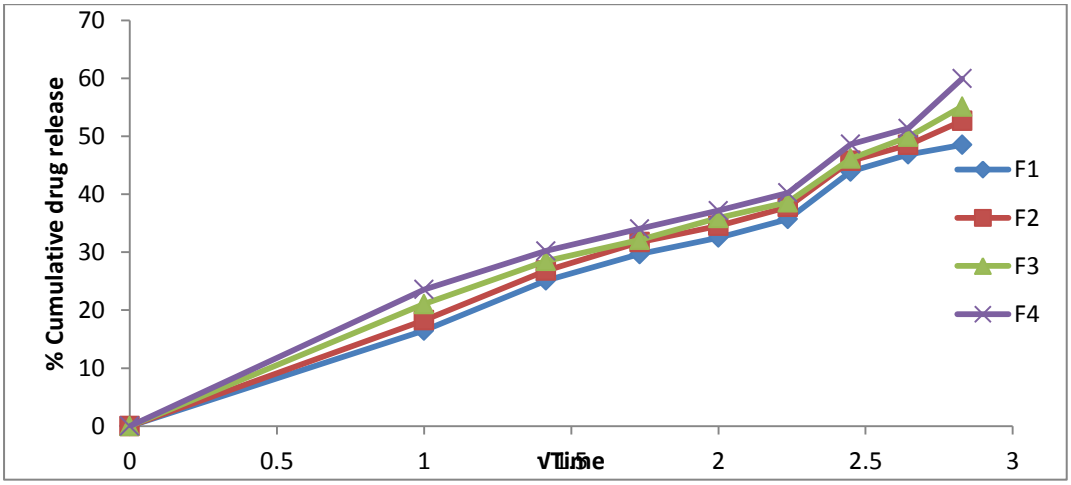
S.No.	Time (hrs)	$\sqrt{T}$	Log T	% Cumulative drug release	% Cumulative drug remain	Log % Cumulative drug release	Log % Cumulative drug remain
1.	0	0	-	0	100	-	2
2.	1	1	0	23.58	76.42	1.37	1.88
3.	2	1.414	0.3	30.22	69.78	1.48	1.84
4.	3	1.732	0.47	34.04	65.96	1.53	1.81
5.	4	2	0.6	37.19	62.81	1.57	1.79
6.	5	2.236	0.69	40.26	59.74	1.60	1.77
7.	6	2.449	0.77	48.64	51.36	1.68	1.71
8.	7	2.645	0.84	51.38	48.62	1.71	1.68
9.	8	2.828	0.9	59.97	40.03	1.77	1.62



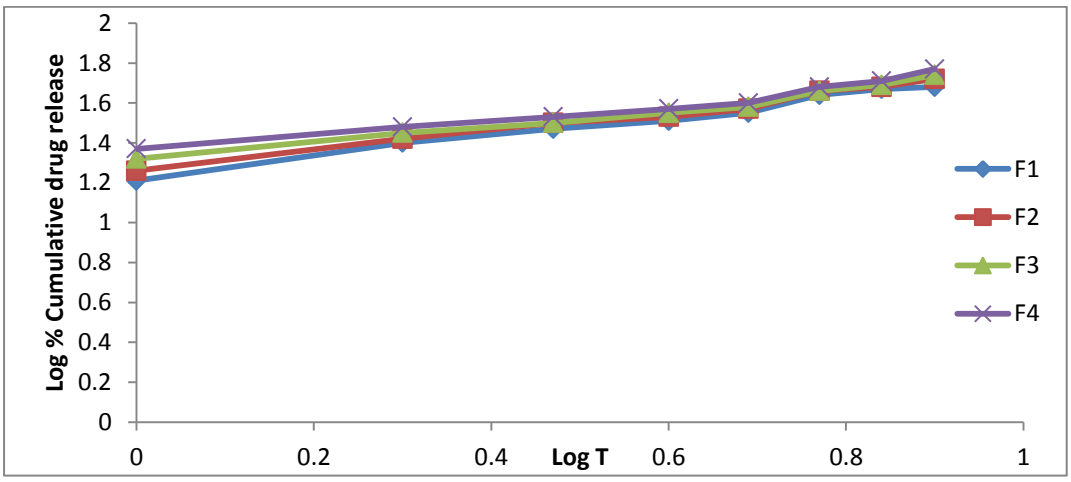
Graph No. 1: Zero order release plot of Tioconazole emulgel



Graph No. 2: First order release plot of Tioconazole emulgel



Graph No. 3: Higuchi plot of Tioconazole emulgel



Graph No. 4: Korsmeyer Peppa's plot of Tioconazole emulgel

Mathematical modeling:

The data obtained from *in- vitro* permeation studies was treated by various conventional mathematical models (zero order, first order, Higuchi and Korsmeyer- peppa's) to determine the

release mechanism from the designed emulgel formulations. Selection of a suitable release model was based on the values of R^2 (regression coefficient), k (release constant) obtained from the curve fitting of release data.

The regression coefficient of the all four formulation F1 to F4 are shown in Table No. 5.18. It was found that all the formulations follows the first order kinetics. The regression coefficients for the all formulations F1 to F4 of Higuchi plot was found to be almost linear.

Table No. 12: Model fitting release profile of Formulation F1 to F4

Formulation code	Correlation coefficient (R^2)			Slope (n) value
	Zero order	First order	Higuchi model	Korsmeyer-Peppas
F_1	0.965	0.955	0.991	0.985
F_2	0.919	0.962	0.992	0.984
F_3	0.910	0.956	0.988	0.973
F_4	0.902	0.948	0.977	0.956

Stability studies:

All the prepared emulgel formulation were found to be stable upon storage for 3 months, no change were observed in their physical appearance.

Table No.13: Stability studies result after 3 months (mean ± SD, n=3) for formulations kept at 37ºc temperature

Formulation	pH	Viscosity	% Drug Content
F_1	6.6±0.23	2388	95. 18
F_3	6.9±0.42	4175	92. 63

Table No. 14: Stability studies result after 3 months (mean ± SD, n=3) for formulations kept at 4ºc temperature

Formulation	pH	Viscosity	% Drug Content
F_1	6.4±0.15	2374	96.51
F_3	6.7±0.34	4159	93.78

CONCLUSION

Considering the various dermatological topical preparation with various advantages and disadvantages it has been concluded that emulgels serve as the better alternative of the present available marketed topical formulation for delivery of hydrophobic drugs. Emulgels also shows good spreadability, better loading capacity ease of application and a good patient compliance. Emulgels having a property of both gels and emulsion and thus it can be used for controlling rate of release of drugs with short half- life. By providing it a gel base they provide stability to the emulsion. Incorporating a various active pharmaceutical ingredients into emulgels is used in treatment of various diseases like fungal infection, as topical anti-inflammatory infection, psoriasis etc. Most of the drugs that are available is also available for topical use are hydrophobic in nature

and which can be easily incorporated into the emulgels and shows stability as well as better drug release. In present days very few marketed emulgel formulation are available in market however it offers a vast field for research and research.However regarding various advantages and future prospective emulgels offer a wide utility in derma care. Because of lack of excessive excipients and oily bases it shows better drug release and thus could be formulation of choice in various dermatological diseases.

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