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Research Article

Design and Evaluation of Topical Oxiconazole Nitrate Emulgel for Fungal Infection

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ABSTRACT

The aim of the present research is to formulate the emulgel of Oxiconazole Nitrate, an antifungal drug for the topical delivery. The formulation was prepared by using carbopol 934, HPMC K4M and xantham gum at different concentration. The formulations were evaluated for compatibility studies, physical appearance, pH, viscosity, spreadability, photomicrography, *in-vitro* studies, antifungal activity, extrudability and stability studies. The prepared formulations were found to be homogeneous. pH and spreadability was found to in the range of 5.6-6.1 and 19.01-26.30 respectively. Among all the formulations (F1-F6), formulation F2 containing carbopol 934 and F5 containing Xanthan gum shown highest drug release (88.18 and 92.51%) after 24 hrs. Antifungal activity of the formulations was assessed by comparing with the marketed ZODERM™E cream. The release studies follow the zero order kinetics. The short term stability studies were conducted for the optimized formulation and it was found to be stable. Hence the oxiconazole emulgel is the promising implement for the antifungal activity.

INTRODUCTION

For decades, delivery of drug through the skin has become a novel approach to achieve both local and systemic effects [1]. Through the transdermal drug delivery system the drug can be targeted to the particular site of action which has significant advantage in improving the clinical importance of the drug by reducing the systemic side effects [2]. Many drugs are targeted through the skin for both local and systemic effects. Lipophilic drug can easily pass through the stratum corneum layer which is the outermost layer of skin compared to the hydrophilic drugs. Hence passage of the drugs through this barrier is the major obstacle in delivering the drugs [3]. Drug delivery across the skin has many advantages such as avoidance of gastro intestinal irritation and also first pass metabolism so that bioavailability can be improved [4].

Semisolid transparent gels are the newer class of dosage forms expanded both in cosmetics and in pharmaceutical preparations.

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Gels are formulated by the entrapment of large amount of aqueous or hydroalcoholic liquid in a network of colloidal solid particles, consisting inorganic substances such as aluminium salts or organic polymers of natural or synthetic origin. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation and to deliver the hydrophobic drugs emulgels came in existence [5]. When gels and emulsions are used in combined form the dosage forms are referred as emulgels. Recently use of novel polymers has been increased, due to their emulsifying and thickening property. They play an important role in decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase of the formulation making them stable. Both oil-in-water and water-in-oil emulsions are used as vehicles to deliver various drugs to the skin. Emulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate the skin. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, water-soluble, longer shelf life, bio-

friendly, transparent and pleasing appearance. Thus Emulgels are proved as a boon in delivery of hydrophobic drugs topically and providing them advantages of gel formulation [6, 7].

Oxiconazole nitrate (OXZ) is a topical antifungal drug used both *in vitro* and *in vivo* in the treatment of tinea corporis, tinea cruris and tinea pedis. *In vitro* oxiconazole is highly effective against many dermatophytes, including *Trichophyton rubrum*, *Trichothyton mentagrophytes*, *Trichophyton tonsurans*, and *Epidermophyton floccosum* [8]. Oxiconazole was shown to be as effective as or more effective than miconazole, clotrimazole, tolnaftate creams, econazole, and bifonazole creams. It has no detectable systemic side effect since only a negligible amount is absorbed from the skin [9]. OXZ is available commercially as creams and lotions. These formulations have disadvantage of less spreading coefficient, sticky nature and less stability. In order to bypass these disadvantages, the topical emulgel formulations have been proposed. The aim of the present research work is to design and evaluate oxiconazole nitrate emulgel for topical fungal disease.

MATERIALS AND METHOD

Oxiconazole nitrate, Carbopol 934, HPMC K4M, Xanthan gum was purchased from Yarrow chemicals, Mumbai, India. Light liquid paraffin, tween 20 and span 20 were purchased from Hi-Media Laboratory Pvt. Ltd, Mumbai, India. Propylene Glycol, Propyl Paraben and Triethanolamine were purchased from Loba cheme Laboratory, Mumbai, India. Methyl paraben was purchased from SD Fine Chem limited, Mumbai, India. All the reagents used were of analytical grade.

Preparation of Oxiconazole Nitrate Emulgel [10-11]

OXZ emulsion was prepared by heat method with minor modification. The oil phase of the emulsion was prepared by dissolving span 20 in liquid paraffin while the aqueous phase was prepared by dissolving tween 20 in purified water. Methyl and propyl paraben was dissolved in propylene glycol where as the drug was dissolved in methanol and both solutions were mixed with the oil phase. Both the oily and aqueous phases was separately heated to 70- 80 °C; then the oily phase was added to the aqueous phase with continuous stirring until cooled to room temperature. The emulsion was poured into gel in ratio 1:1 with gentle stirring until homogenous emulgel was obtained (Table 1).

Characterization of Gellified Emulsion

Drug Excipient Compatibility Study [12]

The sample (0.5 to 1.0 mg) was finely ground and mixed with approximately 100 mg of dry KBr powder. The mixture was then pressed into a transparent disc in an evacuable die at sufficiently high pressure and examined in transmission mode. The IR spectrum of pure OXZ, Polymer and OXZ Emulgel were recorded by FTIR (Fourier-transform infrared) spectrometer (FT/IR-4700, Jasco Int.co.Ltd, Japan).

Physical Examination [13]

The prepared emulgel formulations were inspected visually for their colour, homogeneity, consistency, grittiness and phase separation.

Determination of pH [14]

The pH of emulgel formulations was determined by using digital pH meter (Systronics- Type 335). 1 gm of gel was dissolved in 100 mL of distilled water, it was placed for 2 h and pH was determined.

Rheological Study [13]

The viscosity of the formulated batches was determined using a Brookfield Viscometer (Brookfeild DV-II+ Pro) with spindle 64. The formulation whose viscosity was to be determined was added to the beaker. 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 between 6-60 rpm for 10 min. The viscosity reading was noted.

Spreadability [14]

The spreadability of the gel formulation was determined by taking two glass slides (14*5 cm) of equal length. On one glass slide, 1gm gel was applied. To the other slide, weights (125 g) are added and the time taken for the second glass slide to slip off from the first glass slide was determined. A shorter interval indicates better spreadability. Spreadability was calculated by using the formula,

$$S=M*L/T$$

Where, S = spreadability, M = Weight tied to upper slide, L = Length of glass slides, T = Time taken to separate the slides completely from each other.

Table 1: Formulation of oxiconazole nitrate emulgel

Ingredients	Formulation code					
	F1	F2	F3	F4	F5	F6
Oxiconazole Nitrate	1 g	1 g	1 g	1 g	1 g	1 g
Light liquid paraffin oil	2.5 mL	2.5 mL	2.5 mL	2.5 mL	2.5 mL	2.5 mL
Span 20 & Tween 20	10%					
Propylene glycol	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL
Methanol	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL
Propyl Paraben	0.05 g	0.05 g	0.05 g	0.05 g	0.05 g	0.05 g
Methyl paraben	0.01 g	0.01 g	0.01 g	0.01 g	0.01 g	0.01 g
Carbopol 934	0.5 g	1 g	-	-	-	-
HPMC K4M	-	-	2 g	2.5 g	-	-
Xanthan Gum	-	-	-	-	1.5 g	2 g
Triethanolamine	0.05 mL	0.05 mL	-	-	-	-
Distilled water (qs)	100 mL	100 mL	100 mL	100 mL	100 mL	100 mL

Extrudability Test (Tube Test) [13]

Extrudability test is based upon the determination of weight required to extrude 0.5 cm ribbon of emulgel in 10 sec from lacquered collapsible aluminium tube. The test was performed in triplicate and the average values were calculated. The extrudability was then calculated by using the following formula.

Extrudability = Weight applied to extrude emulgel from tube (g)/Area (cm^2)

Drug Content Determination [14]

Drug content in Gellified emulsion was measured by dissolving 10 mg of Gellified emulsion in 100 mL of solvent (methanol). Absorbance was measured after suitable dilution at 204 nm in UV/VIS spectrophotometer.

Globule Size and Zeta Potential in Emulgel [10]

Globule size and zeta potential of the best formulation was determined by Malvern zetasizer. 1 gm of the sample was dissolved in purified water and agitated to get homogeneous dispersion. Sample was injected to photocell of zetasizer (Zeta sizer Malvern UK based- ZEN 3600). Mean globule diameter and distribution was obtained.

Photomicrography [14]

Morphology of emulsion was studied under light microscope. Best two emulgel formulations were viewed under light microscope to study their shape. The emulgel was suitably diluted, mounted on glass slide and viewed by light microscope under magnification of 40 X.

***In-Vitro* Diffusion Study** [13]

Franz diffusion cell (with effective diffusion area 3.14 cm^2 and 15.5 mL cell volume) was used for the drug release studies. Emulgel (10 mg) was applied on to the surface of cellophane membrane. The cellophane membrane was clamped between donor and receptor chamber of diffusion cell. The receptor chamber was filled with a mixture of freshly prepared phosphate buffer (pH 5.5) and methanol (80:20) solution to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples were collected at suitable time interval and analyzed for drug content by UV visible spectrophotometer at 204 nm after appropriate dilutions.

Drug Release Kinetic Studies [15]

To analyze the mechanism of drug release from the topical gel, the release data were fitted to zero order, first order, Higuchi and Korsmeyer-Peppas equations.

Anti Fungal Activity [10]

Anti fungal activity was checked by using cup plate method. In this method a previously liquefied molten Sabouraud's dextrose agar media was inoculated with 0.2 mL of fungal suspension of Candida albicans having a uniform turbidity. 20 ml of culture medium was poured into sterilized petridish. After complete solidification of liquefied inoculated medium, the wells were made aseptically with cork bore. In each of this plate the formulations F2, F6, and Marketed ZODERM™ cream was placed carefully. Plates were kept for pre diffusion for 30 min. After it normalized to room temperature the

plates were incubated for 48 h. After incubation period was over, the zone of inhibition was measured with the help of Hiantibiotic Zone scale.

Accelerated Stability Studies [14-16]

Best formulations were subjected to stability testing at 40±2°C and 75±5% RH temperature conditions for 2 months. Parameters such as appearance, drug content, phase separation and *in-vitro* diffusion were examined at one month intervals.

RESULTS AND DISCUSSION

Drug Excipients Compatibility Studies

The prominent peak associated with C–Cl (600-800 cm^{-1}), C=N (1615-1700 cm^{-1}), N-O (1500-1560 cm^{-1}), C-H aromatic (3050-3150 cm^{-1}), C-H aliphatic (2850-3000cm^{-1}), C=C aromatic C1400-1600 cm^{-1}), were analyzed. The ranges of peak values were found to be same indicating that there was no interaction of OXZ with different polymers confirming the stability of drug in the formulation as shown in Fig 1.

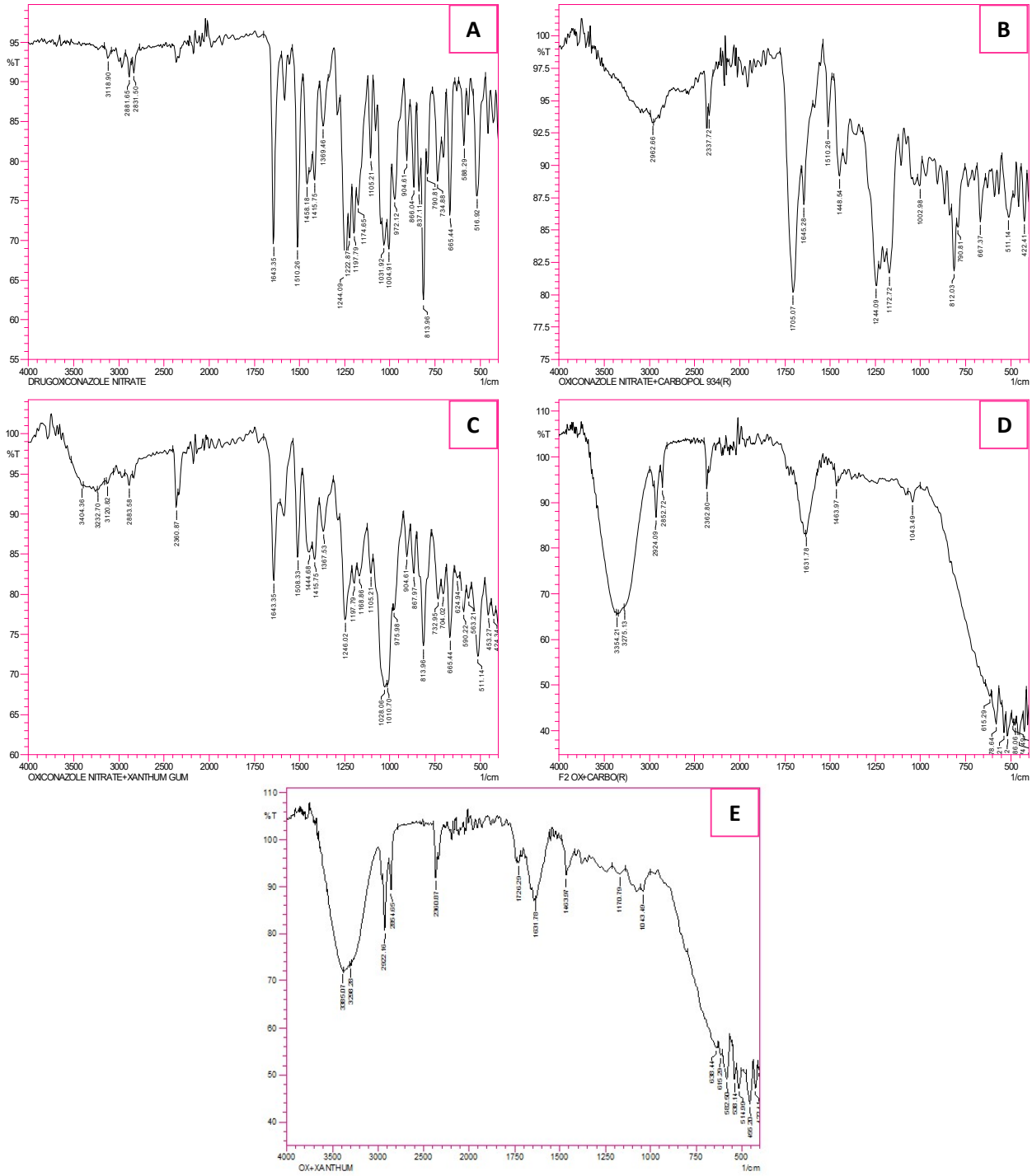


Figure 1: FT-IR spectrum- A: Oxiconazole Nitrate, B: OXZ+Carbopol 934, C: OXZ+Xanthan Gum, D: Formulation F2, E: Formulation F5

Physical Examination

The prepared Gellified emulsion formulations were white viscous preparation with a smooth, homogeneous appearance and there was no phase separation in any of the formulation. Fig. 2 shows the prepared gellified emulsion of OXZ.

Figure 2: Prepared Oxiconazole nitrate **emulgel**

Measurement of pH

The pH values of all prepared formulation ranged from 5.5 to 6.1, which are considered to avoid the risk of irritation upon application to the skin because adult skin pH is 5.5 and it is acceptable if found between 4.8 and 6. The values are given in Table 2.

Rheological Study

Xanthan gum based formulations possessed considerably higher viscosities when compared to carbopol 934 and HPMC K4M as indicated in Table 2. This is due to the difference in the type of gelling agent and its concentration which results in changing the structure and consistency.

Spreadability

F5 showed maximum spreadability whereas F3 showed minimum spreadability. The results (Table 2) indicate that all the polymers used gave emulgels spread by small amount of shear and spreadability of the emulgel decreases with the time.

Drug Content Determination

The drug content of emulgels was estimated spectrophotometrically at 204 nm and drug contents were found in the range of 63.18-92.5 % as shown in Table 2 and Fig. 3 respectively.

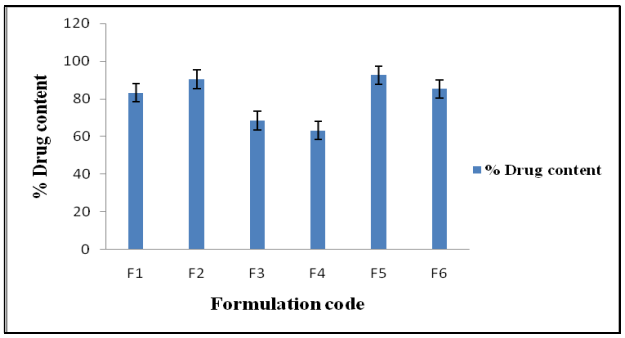


Figure 3: % Drug content of various formulations of emulgel

Globule Size Determination and Zeta Potential of Best OXZ Emulgel

Mean globule size of emulgel F5 was found to be 141.6 d.nm. It confirms the homogeneity of emulgel. Zeta potential of formulation F5 was found to be -30.6 mV. The negative zeta potential indicates that the emulgel have no charge and there is no flocculation in the system which indicates that the system is stable (Fig. 4a & 4b).

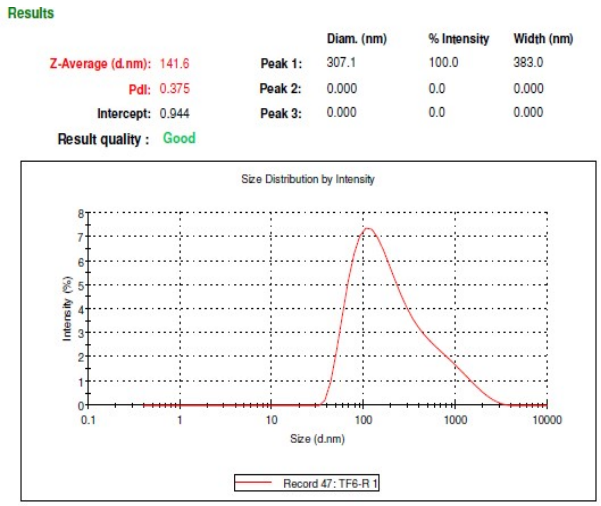


Figure 4a: Globule size determination

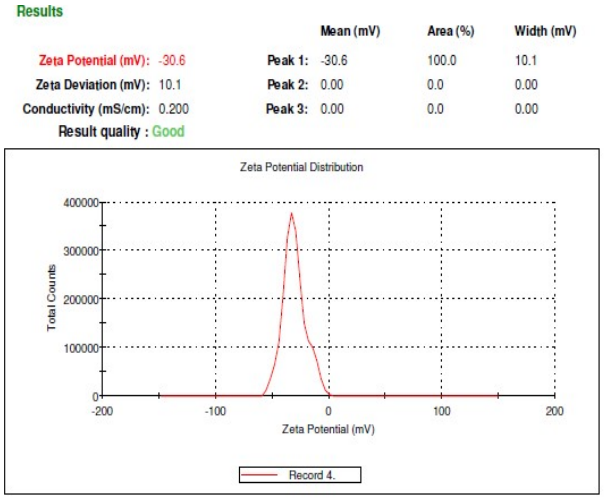


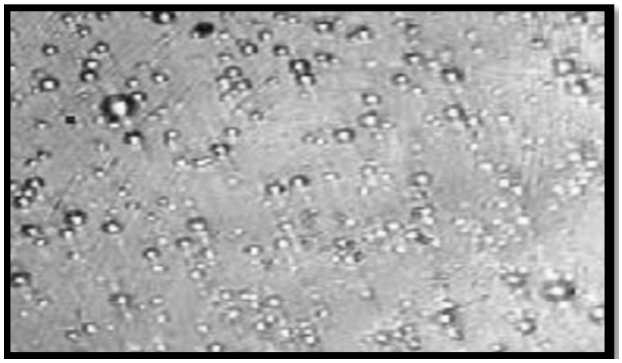
Figure 4b: Zeta potential of OXZ emulgel

Table 2: Characterization studies of various emulgel formulations

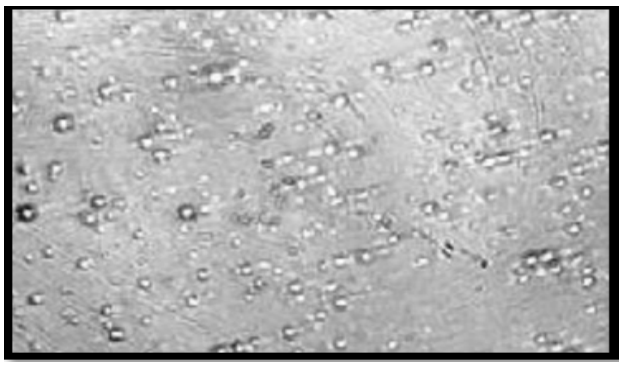
Formulation code	pH	Rheological study (cps)	Spreadability (cm/s)	Extrudability (g/cm²)	% Drug content
	(Mean ± S.D)				
F1	5.6±0.003	24770±1.0	21.65±0.12	21.8±0.5	83.19±0.43
F2	5.5±0.01	28160±1.52	24.33±0.15	23.2±0.45	90.45±0.01
F3	5.6±0.010	8937±2.51	19.01±0.44	17.3±0.64	68.43±0.27
F4	5.8±0.007	9264±1.53	20.37±0.10	17.9±0.3	63.18±0.14
F5	6.1±0.014	83080±2.08	26.31±0.19	24.5±0.26	92.52±0.19
F6	5.9±0.010	86680±2.0	22.93±0.14	25.7±0.47	85.3±0.26

Photomicrography

The suitably diluted emulgels (F2 and F5) were observed under light microscope at 40X as shown in Fig. 5. From the photomicrograph, nearly spherical globules of emulgels were observed indicates there was no coalescence in the system. Hence the system is stable.



(A)



(B)

Figure 5: (A) Photomicrography of formulation F2, **(B)** Photomicrography of formulation F5 under 40x magnification.

In-Vitro Diffusion Study

The better release of the drug from all emulgel formulation can be in the following descending order: F5 > F2 > F6 > F3> F4 > F1 Where the amounts of the drug released after 24 h were 92.51%, 88.18%, 87.11%, 68.34%, 65.37% and 58.13% respectively. F1 showed faster release, this may be due to the lower concentration of the carbopol 934 resulted in faster diffusion of drug through the membrane. Emulgel formulations F3 and F4 (containing HPMC K4M- 2% w/w and 2.5% w/w) shown the release 68.34% and 65.37% respectively after 24 h. The HPMC based formulations showed lowest release which may be due to the lowest entrapment efficiency of the drug in the network like structure of HPMC. Among all formulations F5 (1.5% w/w of Xanthan gum) and F2 (1% w/w of carbopol 934) showed highest release, where as marketed product showed the release of 77.30% at the end of 7 h indicating faster diffusion than the prepared emulgel. So it was evident that as the polymer concentration increases the drug release from the formulation decreases (Fig. 6).

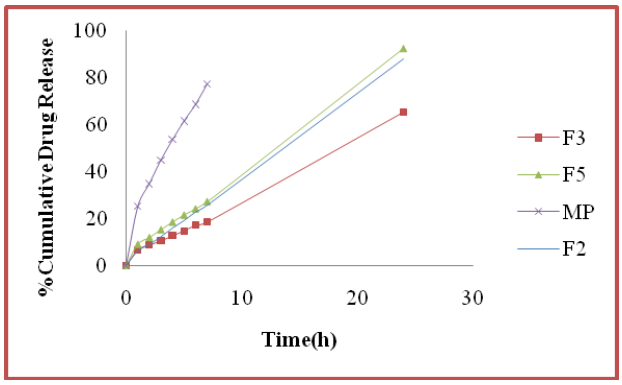


Figure 6: Comparison of *in-vitro* release data of best formulations F5, F2, F3 with marketed ZODERM™E cream

Drug Release Kinetic Studies

The values of correlation-coefficient (r^2) for all the formulations were high enough to evaluate the drug dissolution behavior. The value of release exponent (n) was found to be a function of polymer used and the physicochemical property of a drug molecule itself. Kinetic results revealed that, all the formulations followed Zero order kinetic release as r^2 values (0.994-0.999) are higher than that of other release kinetics and the results were shown in Table 3 and Fig. 7.

Table 3: Kinetic data of Gellified emulsion formulations

Formulation code	Zero order	First order	Peppa's model		Higuchi model	Best Fit Model
			R^2 value	n value		
F1	0.995	0.047	0.250	0.390	0.937	Zero order
F2	**0.999**	**0.978**	**0.872**	**0.167**	**0.885**	**Zero order**
F3	0.994	0.990	0.831	0.182	0.898	Zero order
F4	0.994	0.989	0.846	0.168	0.882	Zero order
F5	0.996	0.973	0.828	0.200	0.890	Zero order
F6	**0.997**	**0.98**	**0.837**	**0.191**	**0.892**	**Zero order**

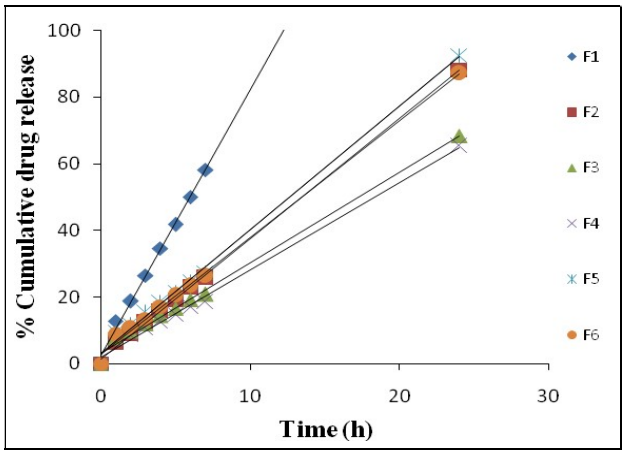


Figure 7: Plot of percentage CDR v/s time (zero order), CDR- Cumulative drug release

Anti Fungal Activity

Zone of inhibition for F2 and F5 was 18 mm and 21 mm respectively. Zone of inhibition for Marketed ZODERM™E Cream was 17 mm. Therefore it can be concluded that the zone of inhibition of prepared emulgels was higher than the marketed formulation of ZODERM™E Cream (Fig. 8).

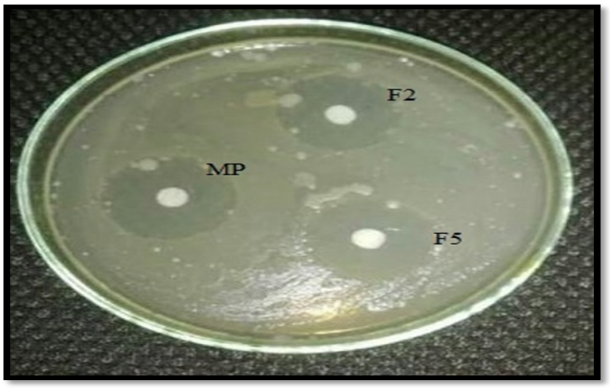


Figure 8: Anti fungal activity of formulation F2, F5 and marketed ZODERM™E cream MP: Marketed Product

Accelerated Stability Studies

Stability studies were carried out on selected formulations F2 and F5 as per ICH guidelines Q1C. The most satisfactory formulations were stored in sealed aluminium tubes at 40 ± 2°C, 75±5% RH for 2 months. There was no change in colour, phase separation and drug content observed during the study. The percentage drug release after 2 months showed 87.62% in F2 and 92.08% in F5 after 24 h indicating no significant changes and emulgels are stable at storage condition. The results were shown in Fig. 9.

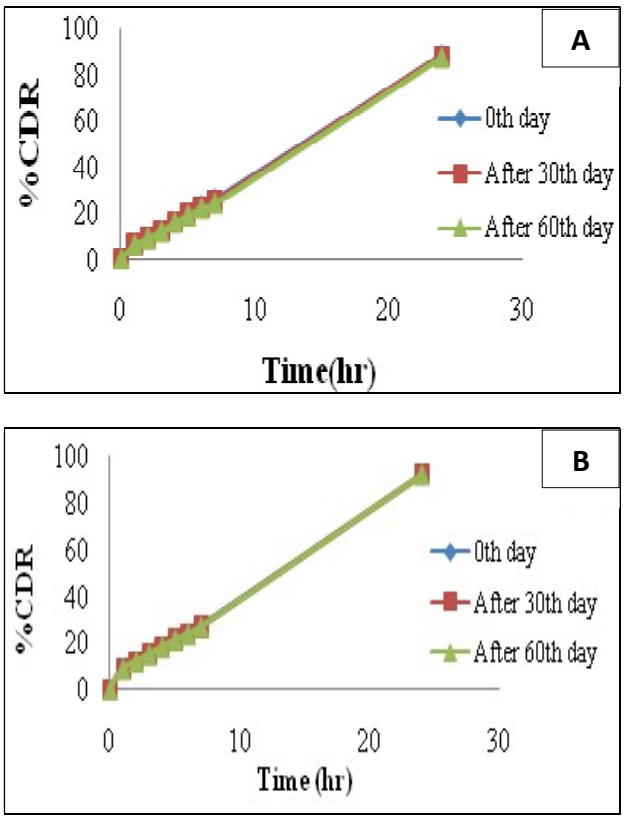


Figure 9: *In-vitro* diffusion data of Formulations **A:** F5 & **B:** F2 after stability studies

CONCLUSION

From the above result we can conclude that Oxiconazole Nitrate Emulsion prepared using different concentration of carbopol 934, HPMC K4M and Xanthan gum showed acceptable physical appearance, rheological property, spreadability, antifungal activity and diffusion

study, which remained unchanged after the stability studies for two months. The present study conclusively proved that the emulgel formulations of Oxiconazole Nitrate prepared using natural polymer Xanthan gum were found to be the best compared with the synthetic one. Emulgel formulation appears to be the promising system for the topical delivery of the hydrophobic drugs in water soluble gel bases.

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REFERENCE

[1] Supriya U, Seema CB, Preeti K. Emulgel: A boon for Dermatological Diseases. Int J Pharm Res and Allied Sci, 2014; 3(4): 1-9.

[2] Barry BW. Novel mechanisms and devices to enable successful transdermal drug delivery. Eur J Pharm Scie, 2001; 14(2):101-14.

[3] Joshi B, Singh G, Rana AC, Saini S, Singla V. Emulgel: A comprehensive review on the recent advances in topical drug delivery. Int Res J Pharm 2011; 2(11): 66-70.

[4] Dev A, Chodankar R, Shelke O. Emulgels: A novel Topical drug delivery system. Pharm and Bio Evaluations, 2015; 2(4): 64-75.

[5] Meenakshi D. Emulgel: A novel approach to topical drug delivery. Int J Pharm Bio Sci, 2013; 4(1):847-56.

[6] Khullar R, Saini S, Seth N, Rana AC. Emulgels: a surrogate approach for topically used hydrophobic drugs. Int J Pharm Bio Sci, 2011 Jul; 1(3):117-28.

[7] Stanos SP. Topical agents for the management of musculoskeletal pain. J Pain Symptom Manag, 2007; 33(3):342-55.

[8] Wu SX, Shen YN, Yan N, Guo NR, Liu LL, Yang JQ. Experimental and clinical investigation on oxiconazole. Chin Med J, 1989; 102(8):644-6.

[9] Jegasothy BV, Pakes GE. Oxiconazole nitrate: pharmacology, efficacy, and safety of a new imidazole antifungal agent. Clin Ther, 1991; 13(1):126-41.

[10] Abeer K, Soha I. Formulation and evaluation of oxiconazole nitrate mucoadhesive Nanoemulsion based gel for treatment of fungal vaginal infection. Int J of Pharm and Pharma Sci, 2016; 8(3): 33-40.

[11] Bhruthika P, Kesha D, Vijeyendra SM. Formulation development and evaluation of microemulsion based hydrogel of econazole nitrate. Int J Pharm Sci, 2014; 5(2):86-107.

[12] Kapadiya B, Gohil D, Patel D, Patel S, Aundhia C, Shah N, Pandya K, Shah C. Formulation and Evaluation of Spironolactone Loaded Emulgel for Topical Application. J Pharm Sci Bio scie Res, 201; 6(5): 740-752.

[13] Mulye SP, Wadkar KA, Kondawar MS. Formulation, development and evaluation of Indomethacin emulgel. Der Pharmacia Sinica, 2013; 4(5):31-45.

[14] Khunt DM, Mishra AD, Shah DR. Formulation design and evaluation of piroxicam emulgel. Int J Pharm Tech Res, 2012; 4(3): 1332-44.

[15] Vikas S, Saini S, Rana AC, Singh G. (a). Development and evaluation of topical emulgel of lornoxicam using different polymer bases. Int Pharm Sci, 2012; 2(3):36-44.

[16] ICH guidelines Q1A (R2). (2003). Stability testing of new drug substances and products.