

FORMULATION AND EVALUATION OF OXICONAZOLE NITRATE EMULGEL FOR TOPICAL DRUG DELIVERY**Prasad S Murade^{1*}, K.R. Jadhav²****¹PG scholar, Department of Pharmaceutics, R.G.Sapkal college of pharmacy, Nashik Maharashtra, India-422212.****²Professor and HOD of Department of Pharmaceutics, , R.G.Sapkal college of pharmacy, Nashik Maharashtra, India-422212.***Corresponding Author's E mail: prasad786.murade.pm@gmail.com

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ABSTRACT

Many years, topical drug delivery has been used to treat skin disorders in specific areas. Emulgel has gained attention as a promising method of topical drug delivery because it combines the benefits of both gels and emulsions. This allows the drug to be delivered directly to the affected site and ensures a prolonged release over time. The main objective of this study was to improve the delivery of a hydrophobic drug called Oxiconazole nitrate by formulating it into an emulgel. Various excipients such as Tween 80, Span 80, Light Liquid Paraffin, Carbomer 934, Propyl Glycol, Isopropyl Myristate, Cetosteryl Alcohol, Methanol, and Water were used in the formulation. The resulting formulation was then evaluated for its physical properties, drug content, pH determination, antifungal activity, and kinetic modeling. A 3² factorial design was applied to optimize the formulation, and based on the results; the F3 batch was selected as the optimized formulation. This optimized batch was further subjected to stability testing for a period of 45 days.

Keywords: Emulgel, Prolong Release, Oxiconazole, Stability Study.

INTRODUCTION

Oxiconazole is a well-known antifungal agent used to treat various skin diseases caused by fungi, such as ringworm of the body, ringworm of the foot (athlete's foot), and ringworm of the groin (jock itch). It is available in topical forms like gels, creams, and ointments^{1,2}. Oxiconazole Nitrate, the salt form of Oxiconazole, is commonly used topically due to its high lipophilicity. However, its hydrophobic nature limits its diffusion when formulated as a cream or gel. To improve skin permeation and patient compliance, the formulation of an emulgel is beneficial. In emulgels, the oil phase used to dissolve the drug is light liquid paraffin³.

Both oil-in-water and water-in-oil emulsions are widely used for their therapeutic properties and as vehicles for delivering drugs to the skin. Emulsions offer elegance, easy washability, and high skin penetration ability⁴. Oil-in-water emulsions are more commonly used for treating dry skin and as emollients, while water-in-oil emulsions are suitable as water-washable bases and for cosmetic purposes⁵.

Gels possess advantageous characteristics for dermatological use, such as thixotropic behavior, being greaseless, easy spreadability, easy removal, emollient properties, non-staining, compatibility with various excipients, and water solubility or miscibility⁶.

Emulgels are a combination of emulsions (oil-in-water or water-in-oil) with a gelling agent, resulting in gel-like consistency. They combine the benefits of both emulsions and gels, making them highly accepted by patients⁷. Emulgels have been increasingly used for delivering different medications to the skin and are also known as creamed gel, quasi emulsion, or gelled emulsion. The main objective of this study is to formulate a 1.0% w/w Oxiconazole nitrate emulgel and optimize the formulation through in-vitro and ex-vivo diffusion studies using a 3² factorial design model and kinetic modeling⁸.

MATERIALS AND METHODS

Preparation of Oxiconazole nitrate Emulgel:

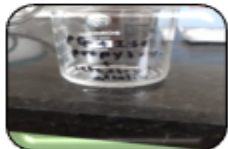
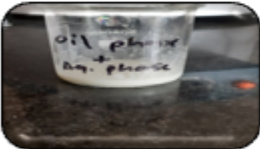
1. First, the gel was prepared by dispersing Carbopol 934 in heated purified water (80 °C), and the dispersion was cooled and left overnight. 
2. The oil phase of the emulsion was prepared by dissolving Span 80 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 80 in purified water. 
3. Cetosteryl alcohol and Isopropyl myristate were dissolved in propylene glycol whereas Oxiconazole nitrate was dissolved in methanol, and both solutions were mixed with the aqueous phase. 
4. 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 cooled to room temperature. 
5. The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the emulgel. 

Figure 1: Method of Preparation of Oxiconazole nitrate Emulgel

Characterization of Emulgel

Physical appearance (11-26)

For visual inspection, the emulgel formulations were examined for their pH, color, homogeneity, consistency, grittiness, and phase separation.

Measurement of pH

The pH measurement was conducted using a pH meter (Labman pH system LMPH-10) that was calibrated with standard buffer solutions of pH 4, 7, and 9. A sample of approximately 0.5g of the emulgel was weighed and dissolved in 50.0ml of distilled water, and its pH was measured.

FTIR spectra

Analysis was performed on Oxiconazole nitrate using Shimadzu IRAffinity-1. The spectrum was recorded using potassium bromide (KBr) as a blank, with a resolution of 4cm⁻¹ over a range of 400-4000cm⁻¹. The peaks observed in the spectrum of Oxiconazole nitrate were compared with the characteristic peaks reported in the monograph. In summary, the emulgel formulations were visually inspected for their physical properties, pH was measured using a pH meter, and FTIR spectroscopy was used to analyze the composition of Oxiconazole nitrate.

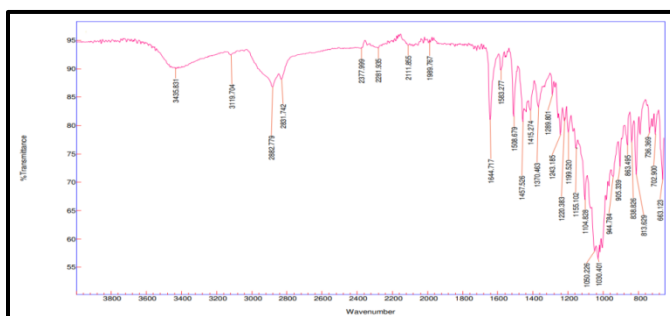


Figure 2: IR of Oxiconazole nitrate

Viscosity

The viscosity of the emulgel was determined using a Brookfield Viscometer (Amtech Model Number: LVDVE) with spindle number 64. The spindle was rotated at different speeds of 10, 50, 60, and 100 rpm. Viscosity (cP) and torque (%) were measured during the rotation. Lower torque values indicate better viscosity.

Drug content determination:

To determine the drug content, an emulgel sample equivalent to 10mg of Oxiconazole nitrate (1g of emulgel) was taken in a 10ml volumetric flask. 5ml of solvent (Methanol) was added, and the volume was made up to the mark with solvent (Methanol), resulting in a concentration of 1000µg/ml. An

aliquot of 0.1ml was transferred to another 10ml volumetric flask, and the volume was made up with solvent (Methanol). The absorbance of the prepared solution was measured at the wavelength of maximum absorption (λ max) of 242nm using a UV-visible spectrophotometer.

In vitro diffusion test:

A laboratory setup resembling a Franz diffusion cell was used to analyze the release pattern of a drug from an emulgel through an in vitro diffusion test. The setup consisted of two compartments, namely the donor and receptor compartments, with a cellophane membrane placed in between as a diffusion barrier. The donor compartment, with a diameter of 24 mm, was open to the atmosphere on one end, while the receptor compartment allowed for sample collection. The phosphate buffer solution with a pH of 5.8 (PBS) served as the diffusion medium. A 10 mg emulgel containing the equivalent amount of the drug was placed on the drug release membrane in the donor compartment. The donor and receptor compartments were securely joined using a clamp, and the assembly was placed on a magnetic stirrer. The receptor compartment, containing 25 ml of PBS, was kept at a constant temperature of $37 \pm 0.5^\circ\text{C}$ and stirred at a rate of 50 rpm. At specific time intervals, 1 ml samples were withdrawn and diluted with methanol as a solvent. The drug content in the samples was analyzed using a UV spectrophotometer at the wavelength of maximum absorption (λ max) of 242 nm, compared to a blank sample. The receptor phase was replenished with an equal volume of phosphate buffer each time a sample was withdrawn.

7. Antifungal test:

Step 1: Media preparation:

- Prepared Mueller Hinton Agar (M173) plates for the Kirby Bauer method, which is used to test the susceptibility of rapidly growing aerobic organisms.
- To accommodate fastidious organisms like *Aspergillus niger* and *Candida albicans*, Mueller Hinton Agar (M173) was supplemented with 5% sterile defibrinated blood.
- For fungal cultures, the medium used was Mueller Hinton Agar (M173) supplemented with 2% glucose and 0.5mcg/ml methylene blue dye (GMB medium). The agar in the plates needed to be sterile and have a depth of approximately 4-5mm.

Step 2: Inoculum Preparation

- For fungal cultures involved selecting five distinct colonies, each around 1mm in size, from a 24-hour-old culture grown on Sabouraud Dextrose Agar (M063). These colonies were then incubated at a temperature of $35\pm 2^{\circ}\text{C}$.

Step 3: Test procedure:

- It included dipping a sterile non-toxic cotton swab into the standardized inoculum, which was adjusted to achieve confluent growth on the petri plate.
- The soaked swab was firmly rotated against the upper inside wall of the tube to remove excess fluid.
- This process was repeated three times, and the entire agar surface of the plate was streaked with the swab, turning the plate at a 60° angle between each streak.
- After streaking, the inoculum was allowed to dry for 5-15 minutes with the lid in place.
- Aseptic technique was used to apply the discs, which were deposited on the plate with their centers at least 24 mm apart.
- However, for fastidious organisms and certain antibiotics, such as penicillins and cephalosporins, the discs should preferably be placed with their centers 30mm apart.
- For fungal cultures, the plates were immediately incubated at $35\pm 2^{\circ}\text{C}$ and examined after 20-24 hours of incubation.
- The resulting zones of inhibition would be uniformly circular, and there would be a semi-confluent lawn of growth if the plate was streaked correctly.
- If there was insufficient growth after 24 hours of incubation, the plates were read at 48 hours.

Kinetic Modelling study

The utilization of mathematical modelling offers significant advantages as it allows for the prediction of release kinetics before implementing release systems. This approach facilitates the measurement of important physical parameters such as the drug diffusion coefficient and involves fitting models to experimental release data. Therefore, mathematical modelling plays a crucial role in optimizing the formulation process by considering all factors that influence drug release kinetics.

Model-dependent methods rely on mathematical functions to describe the dissolution profile. Once a suitable function is chosen, the dissolution profiles are evaluated based on the model parameters

derived from it. Some commonly used model-dependent approaches include zero order, first order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas models.

Accelerated stability studies as per ICH Guidelines

To comply with the guidelines outlined by the International Council for Harmonisation (ICH), accelerated stability studies were conducted for the optimized batch. These studies aimed to assess the impact of formulation additives on drug stability and to evaluate the physical stability of the formulation under accelerated storage conditions. The optimized batch was exposed to elevated temperature and humidity conditions ($40 \pm 2^\circ\text{C}$ / $75 \pm 5\%$ RH). Samples were taken at intervals of 0, 30, 60, and 90 days to assess physical appearance, pH, and drug content.

RESULT AND DISCUSSION

In the present work, an attempt was made to formulate and evaluate topical hydrogel drug delivery systems. The objective was to modify drug absorption and exposure to improve pharmacokinetics and pharmacodynamics by controlling the rate of drug release from the dosage forms. The emulgel formulations had an off-white color, no discernible odor, and a microcrystalline powder-like appearance. The pH of the gel formulations ranged from 6.00 ± 0.1 to 6.25 ± 0.1 , which falls within the normal pH range of the skin and is therefore unlikely to cause any skin irritation. The spreadability of all the formulated batches was evaluated and found to be within the range of 10.6 – 14.8 gm.cm/sec. With an increase in the concentration of Carbopol 934, the viscosity increased, leading to a decrease in the spreadability of the formulated gel. The specific results for spreadability can be found in Table 2. The viscosity of all the formulated batches was analyzed and found to be within the range of 5183 – 7356 cP (centipoise). As the concentration of Carbopol 934 increased, the viscosity also increased. All the formulated batches were examined for drug content determination and results were found in range of 97.25 – 102.32 % which compiles the limit 95-105% as per literature. The results were expressed in table 1.

Table 1: Evaluation of Oxiconazole Nitrate Emulgel

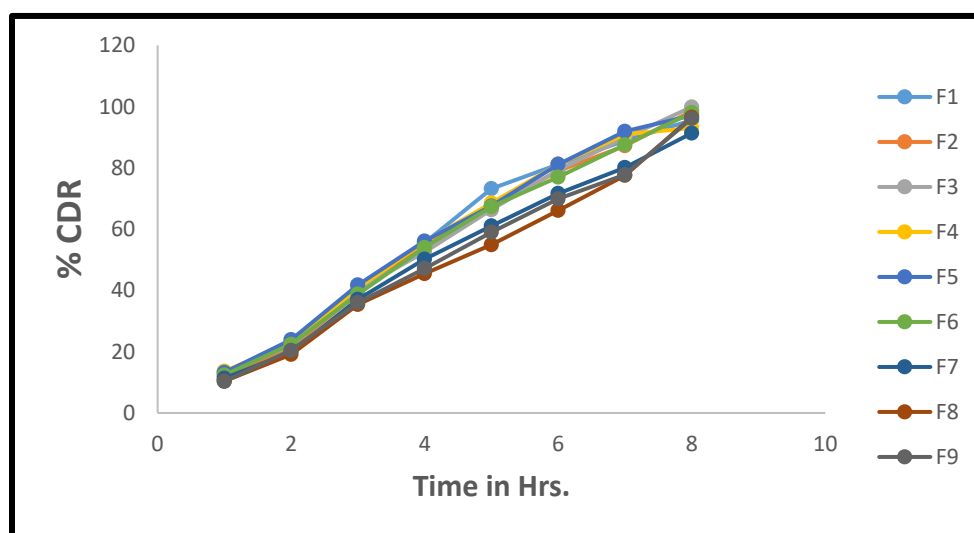
Batches	pH	Spreadability (gm.cm/sec)	Viscosity (cP)	Drug content (%)
F1	6.21 ± 0.1	14.8 ± 0.2	5476 ± 124	97.35
F2	6.09± 0.1	14.2 ± 0.1	5241 ± 115	98.71
F3	6.05± 0.1	13..5 ± 0.2	5183 ± 174	99.14
F4	6.00 ± 0.1	12.6 ± 0.2	6988 ± 87	101.55
F5	6.17 ± 0.1	11.8 ± 0.2	6754 ± 101	102.32
F6	6.18 ± 0.1	11.5 ± 0.1	6539 ± 55	97.75
F7	6.15 ± 0.1	10.6 ± 0.2	7356 ± 98	98.33
F8	6.19 ± 0.1	10.9 ± 0.1	7232 ± 112	97.25
F9	6.25± 0.1	10.6± 0.1	7198 ± 55	98.78

Determination of Drug release (Drug diffusion):

The drug diffusion characteristics of all the formulated batches were examined, and the results ranged from 91.34% to 99.87%. As the formulation's viscosity increased and the concentration of surfactant decreased, the drug diffusion process slowed down over time, leading to a longer-lasting effect. The in vitro drug release study results, presented in Table 2 and Figure 3, indicated that formulation F3 exhibited sustained release of the drug, with the highest diffusion rate of 99.87% after 8 hours. Formulations F1, F4, and F 7 also demonstrated sustained drug release but were unable to release the full dose of the drug within 8 hours. This can be attributed to the lower levels of surfactant and higher levels of viscosity-modifying polymer in these formulations. Among the nine formulations, formulation F3 achieved the maximum release after 8 hours, with 99.87% of the drug available for antifungal activity.

Table 2: Determination of % drug diffusion

Time (Hrs.)	Batches →	% Cumulative Drug Release (%)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1		10.91	12.2	13.33	13.63	13.23	12.4	11.33	10.4	10.3
2		21.02	21.44	21.89	22.91	23.91	22.44	19.91	19.11	20.44
3		41.54	38.99	40.43	40.8	41.8	38.79	37.1	35.42	36.03
4		55.53	55.02	52.53	55.81	56.11	54.02	50.21	45.47	47.16
5		73.2	67.14	66.33	68.53	67.53	67.34	61.03	54.91	59.15
6		81.14	78.99	79.32	81.14	81.14	76.99	71.64	66.11	69.89
7		88.92	87.2	89.78	90.92	91.92	87.5	80.11	77.53	77.78
8		95.53	98.52	99.87	93.23	97.09	98.44	91.34	96.53	96.13

**Fig 3: % CDR vs Time for drug diffusion****Antifungal testing of optimized batch:**

The antifungal study was conducted following the standard procedure outlined in the experimental work. The optimized batch of emulgel exhibited a zone of inhibition measuring 36 mm, indicating significant antifungal activity. In comparison, the standard antifungal agent (Nystatin) displayed a zone of inhibition measuring 27 mm. Based on these antifungal results, it was confirmed that the optimized emulgel batch possessed satisfactory antifungal activity. The detailed results can be observed in Figure 4 and Table 3.

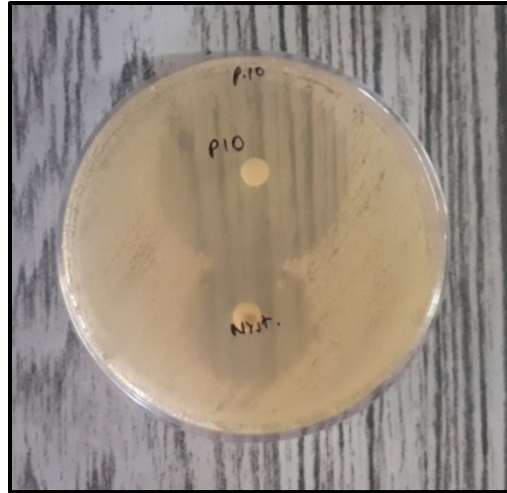


Fig 4: Antifungal plate

Table 3: Result of Anti fungal test

Sr.no.	Sample	Zone of inhibition (mm)
1.	Optimized batch (F3)	36mm
2.	Standard agent for antifungal activity (Nystatin)	27 mm

Kinetic Modeling Study:

The optimized batch of Emulgel underwent a kinetic modeling study using various models including Zero order, First order, Higuchi model, Korsmeyer-Peppas model, and Hixon-Crowell model. The results obtained from the modeling study are provided below.

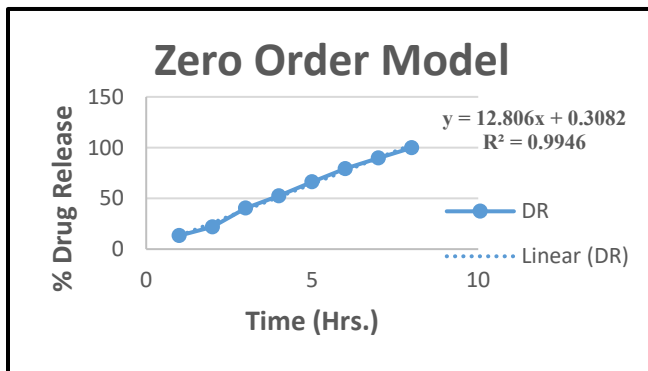


Fig 5: Zero Order Model

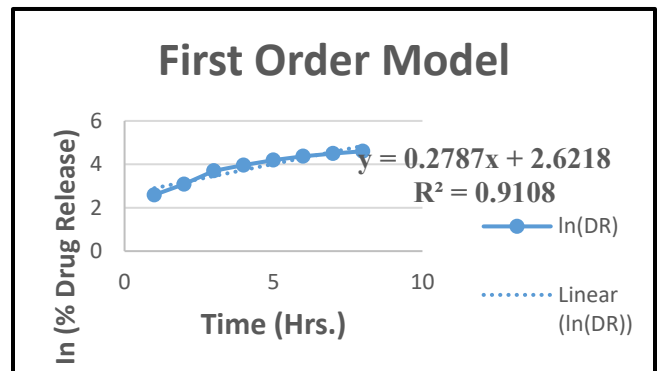


Fig 6: First Order Model

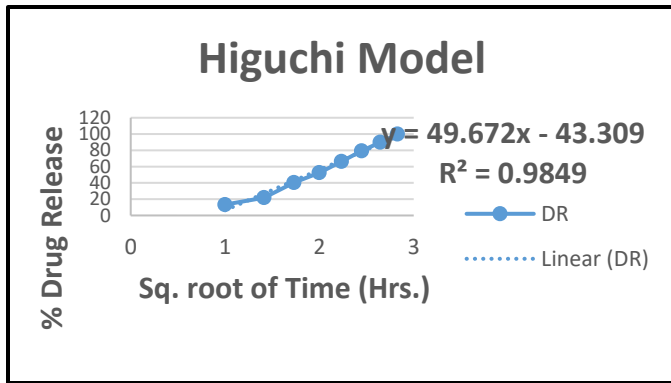


Fig 7: Higuchi Model

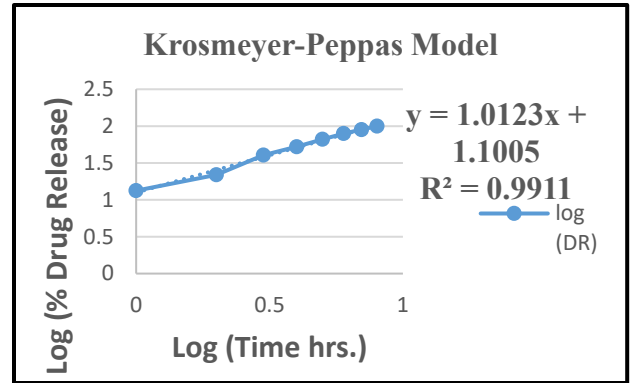


Fig 8: Krosmeyer-Peppas Model

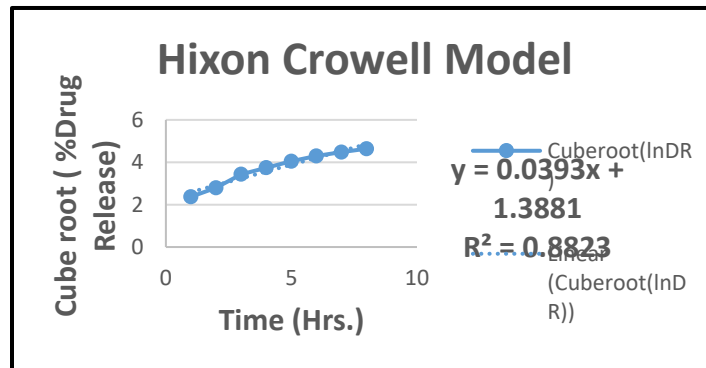


Fig 9: Hixon-Crowell Model

Stability Study:

Significant changes were not noticed. The optimized formulation was found to be stable after exposure to accelerated temperature and humidity conditions for a period of 3 months. No significant changes were seen in physical evaluation parameters and given in the Table 4.

Table 4: Stability Study of optimized formulation

Evaluation parameters	Results
Colour	White
Odour	Characteristic
Appearance	Smooth
pH	6.01
Viscosity	5215 cP
Drug content	98.85 %
Drug diffusion	98.56

CONCLUSION:

Among all the formulations, the emulgel prepared with 7% Light Liquid Paraffin and 1% Tween 80 exhibited superior overall product qualities. The emulsion system in the formulation facilitated the solubilization of hydrophobic drugs, thereby improving their availability in the formulation. Comparing the emulgel with a marketed gel, the emulgel demonstrated better drug release, permeation, and appearance, making it more acceptable. The drug release from the emulgel followed a Zero-Order kinetic model, and in vitro diffusion studies showed significant drug release for up to 8 hours. In-vitro diffusion studies showed good percent drug release upto 8 hrs. The formulated emulgel showed no irritation after performing skin irritation test. The percentages of Carbopol 934 and Span 80 in the formulation had an impact on the drug diffusion. As the percentage of Carbopol 934 increased, diffusion decreased, while an increase in the percentage of Span 80 led to increased diffusion. Span 80 had a stronger impact on diffusion compared to Carbopol 934, as indicated by its lower p-value. Based on the evaluation of batches and factorial design model study, batch F3 was selected as the optimized batch. Overall, the results of this study clearly demonstrate that Oxiconazole nitrate emulgel can be a favorable alternative to conventional dosage forms. However, further clinical studies are required to evaluate the efficacy of this system. Taking all these factors into consideration, it can be concluded that the objectives of the present research study were successfully achieved.

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