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Formulation and Characterization of Oxiconazole-Loaded Emulgel for Topical Drug Delivery

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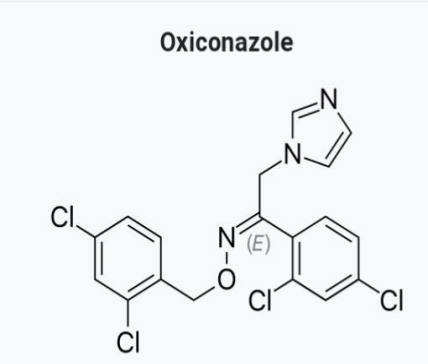
Abstract: *This study aimed to develop an Emulgel formulation of Oxiconazole nitrate, a hydrophobic, broad-spectrum antifungal agent used to treat superficial fungal infections. Emulgel, with its dual release control systems of emulsion and gel, was employed to enhance the drug's bioavailability. The Emulgel formulations were characterized for various parameters, including pH, viscosity, spreadability, extrudability, in vitro drug release, skin irritation on Wistar rats, and in vitro antifungal activity against Candida albicans. The optimized formulation (F5) exhibited 92.06% drug release over 12 hours, showed no skin irritation, and demonstrated superior antifungal activity compared to a marketed cream containing Oxiconazole nitrate.*

Keywords: Emulgel, Oxiconazole, imidazole.

I. INTRODUCTION

Oxiconazole is a broad-spectrum imidazole antifungal agent. It has demonstrated the ability to inhibit DNA synthesis and reduce intracellular adenosine triphosphate levels. Like other imidazole antifungals, it can enhance membrane permeability to zinc, increasing its cytotoxicity. It falls under the biopharmaceutical classification system as a Class II drug due to its low aqueous solubility and poor systemic absorption. The primary drawback of this drug lies in its low aqueous solubility and hydrophobic nature. Consequently, various techniques, including the use of surfactants, cosurfactants, cosolvents, and more, are employed to enhance its solubility. Topical drug delivery systems have been utilized for centuries to administer both local and systemic treatments.

Transparent gels have gained widespread use in cosmetics and pharmaceutical preparations. However, they face a significant limitation in delivering hydrophobic drugs. Emulsions, while effective for hydrophobic drugs, are thermodynamically unstable. Emulgel offers an improved solution for delivering hydrophobic drugs like oxiconazole by increasing their solubility and providing dual-controlled release through the incorporation of two systems: emulsion and gel. This approach overcomes the disadvantages of both gel and emulsion. Emulgel is characterized by its greaseless nature, easy spreadability, thermodynamic stability, long shelf life, and improved patient compliance.



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II. MATERIALS AND METHODS

Materials

Source of Chemicals:

1. Oxiconazole: Gift sample from Harman Finochem Pvt., Ltd., Aurangabad.
2. Carbopol 981: Purchased from Lubrizol, Mumbai.
3. Tween 20, Span 20, propylene glycol (PEG), carbopol 940, methylparaben: Purchased from Hi-Media Pvt., Ltd., Mumbai.
4. Methanol and triethanolamine: Purchased from SD Fine Chem. Pvt., Ltd., Mumbai.
5. Glycerol: Purchased from Ranbaxy, Mumbai.
6. Propylparaben: Purchased from Priya Research Labs, Bangalore.

Methods Preformulation study

In the preformulation study for drug authentication, the following methods and analyses were employed:

1. Melting Point Determination:* The melting point of oxiconazole was determined using the capillary tube method.
2. Compatibility Testing:* The compatibility of oxiconazole nitrate with various polymers and excipients was assessed through infrared (IR) analysis. IR spectral analysis was conducted using the potassium bromide method. Samples included the drug, individual polymers, and a mixture of the drug with each polymer.
3. Differential Scanning Calorimetry (DSC) Analysis:* DSC analysis was performed using a DSC 60 detector (Shimadzu, Co., Japan). Approximately 5 mg of oxiconazole and a physical mixture of oxiconazole with Carbopol 981 and Carbopol 940 were weighed into an aluminum pan, sealed, and subjected to DSC scanning. The scan ranged from 30°C to 300°C at a heating rate of 10°C/min under a nitrogen purge, with an empty pan used as a reference.
4. Saturation Solubility Testing:* The saturation solubility of oxiconazole nitrate was measured in various oils, including castor oil, liquid paraffin oil, oleic acid, and olive oil. Additionally, saturation solubility was determined in various surfactants such as Span 20, Span 80, Tween 20, Tween 60, and Tween 80, as well as in various cosurfactants, including PEG 400, PEG, and PEG 600.

III. PREPARATION OF EMULGEL

1. Dissolve oxiconazole nitrate in surfactant, cosurfactant, and oil.
2. Prepare the oil phase by dissolving Span 20 in light liquid paraffin.
3. Prepare the aqueous phase by dissolving Tween 20 in purified water.
4. Heat both phases separately to 70°C–80°C.
5. Add the oil phase to the aqueous phase with continuous stirring until it cools to room temperature.
6. Mix the obtained emulsion with gel at a 1:1 ratio with continuous stirring to create the emulgel.

Emulgel Formulation:

Incorporate the emulsion, equivalent to 1% of oxiconazole nitrate, into a gel base that was prepared by soaking a gelling agent in water overnight.

IV. EVALUATION OF EMULGEL

- Physicochemical Properties: Inspect the emulgel visually for color, homogeneity, and consistency.
- Photomicroscopy: Study the globular structure of the optimized formulation under a microscope.
- Drug Content: Dilute emulgel, measure absorbance at 212 nm, and calculate drug content using a standard calibration curve.
- pH Measurement: Determine the pH of emulgel formulations using a digital pH meter.
- Viscosity: Measure the viscosity using a Brookfield viscometer at 50 rpm.
- Spreadability: Measure the diameter of a circle formed by emulgel on a glass plate after a glass plate is dropped from a height of 5 cm.

These evaluations ensure the emulgel's quality and suitability for its intended use.

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V. PREFORMULATION STUDY

In the preformulation study for drug authentication:

1. Melting Point Determination:

- Melting point of oxiconazole was determined using the capillary tube method.

2. Compatibility Testing with Polymers and Excipients:

- Compatibility of oxiconazole nitrate with polymers and excipients was established through infrared (IR) spectral analysis.
- IR spectral analysis was performed using the potassium bromide method. Samples included the drug, polymers, and mixtures of the drug with each polymer.

3. Differential Scanning Calorimetry (DSC) Analysis:

- DSC analysis was conducted using a DSC 60 detector from Shimadzu, Co., Japan.
- Approximately 5 mg of oxiconazole and physical mixtures of oxiconazole with Carbopol 981 and Carbopol 940 were weighed into aluminum pans and sealed.
- DSC scans were recorded from 30°C to 300°C at a heating rate of 10°C/min under a nitrogen purge, with an empty pan as a reference.

4. Saturation Solubility Testing:

- Saturation solubility of oxiconazole nitrate was measured in various oils, including castor oil, liquid paraffin oil, oleic acid, and olive oil.
- Saturation solubility of oxiconazole nitrate was also measured in various surfactants, such as Span 20, Span 80, Tween 20, Tween 60, and Tween 80.
- Additionally, saturation solubility of oxiconazole nitrate was determined in various cosurfactants, including PEG 400, PEG, and PEG 600.

VI. PREPARATION OF EMULSION

The required quantity of oxiconazole nitrate was dissolved in surfactant, cosurfactant, and oil. The oil phase of the emulsion was prepared by dissolving Span 20 in light liquid paraffin, and aqueous phase was prepared by dissolving Tween 20 in purified emulsion.

CONTENT	CONCENTRATION(%)
Oxiconazole Nitrate	1 (w/v)
Poloxamer 407	22 (w/v)
Ethanol	18 (v/v)
PEG 400	9 (v/v)
Diatilled water	q.s.

Both the oil phase and aqueous phase were separately heated to 70°C–80°C, then the oil phase was added into the aqueous phase with continue stirring until it cools to room temperature. The obtained emulsion was mixed with gel at 1:1 ratio with continuous stirring to obtain the emulgel.[7] The gel base was prepared by soaking the gelling agent overnight in a sufficient quantity of water, and then, the emulsion equivalent to 1% of oxiconazole nitrate was incorporated in the gel base to give the emulge **Fig-**Preparation of Emulsion

In vitro antifungal analysis

The preparation of Candida strains The strains of Candida albicans ATCC 10231, Candida krusei ATCC 6258 and Candida parapsilosis ATCC 22,019 were prepared to 0.5 MacFarland turbidity standard (1–5 × 106 CFU/mL) in 0.9% NaCl. These solutions were 1000-fold diluted to 1–5 × 103 CFU/mL.

Broth macrodilution To get reliable data on in vitro antifungal efficiency of ON and TGF, an antifungal analysis was applied within a broth macrodilution method according to CLSI, 2008a, CLSI, 2008b standard guidelines. Due to the lack of information about ON in the guidelines, modified azole standards and methods were used. As a solvent, DMSO is a best choice except fluconazole, which also worked excellently for ON and TGF, as previously reported (Gebhart et al., 1984). Because of the evaluation of dilution range is not clear for oxiconazole, the widest range in CLSI guidelines (0.016–128 mg/L) with 14 serial dilutions and also positive and negative control tubes were applied. Following the addition of RPMI medium and Candida solutions, final concentrations were 100-fold diluted. The tubes were incubated

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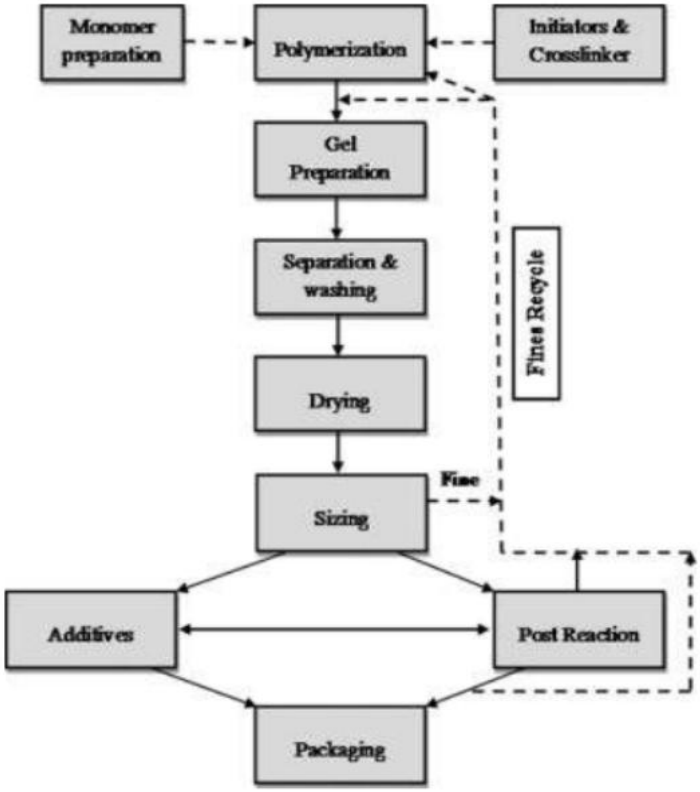
in ambient atmosphere and 37 °C temperature for 24 h, and visual evaluation was done to detect minimum inhibitory concentration (MIC) levels (CLSI, 2008a, EUCAST, 2015). Furthermore, to evaluate the minimum fungicidal concentration (MFC), visual turbidity-detected tubes were additionally inoculated to standard methods agar (SMA) (Thermo-Fisher Scientific, MA, USA) quantitatively (1 µL, 10 µL), as applied previously by Cantón et al., (2003). For MFC, fungicidal rate of ≥98% is necessary and according to this data, tubes with a maximum of 20 colonies for 10 µL and 2 colonies for 1 µLinoculation were accepted as MFC (CLSI, 2009, Balouiri et al., 2016, Arendrup et al., 2010, Pfaller et al., 2008, EUCAST, 2008).



The time-dependent fungicidal activity The method modified from CLSI M26-A guidelines was applied to compare the fungicidal activity alterations of ON and TGF in time (CLSI M26-A, 1999). 40 µL from each previously prepared stock solutions were added to 3960 µL RPMI media (100-fold diluted). Then, 2.225 mL from this solution were added into 29.775 mL RPMI media, which results final concentrations to 8.9 µg/mL. With the same methodology in broth macrodilution, serial dilutions were made at 8.9, 4.45, 2.225, 1.1125, 0.5563, 0.2781 and 0.1391 µg/mL final concentrations.

Solutions of Candida species ATCC 10,231 at 0.5 MacFarland turbidity standard (1–5 × 106 CFU/mL) was 10-fold serially diluted. After combining fungal and antifungal solutions, the concentrations of ON and TGF were finally at 8, 4, 2, 1, 0.5, 0.25 and 0.125 µg/mL.

At 0, 4, 8, 16 and 24th h, 1 µL and 10 µL from each tube were quantitatively inoculated to SMA and plates were incubated in ambient atmosphere at 35 °C temperature for 24 h. Colonies were counted and noted (Cantón et al., 2003, CLSI, 1999, Klepser et al., 1998, Clancy et al., 2006, Moore et al., 2001, Ernst et al., 2000).[11][12]

Claims

Microemulsion Gel Preparation of Oxiconazole Nitrate

In this microemulsion gel preparation, Oxiconazole Nitrate is combined with a blank gel. The composition is as follows:

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For Oxiconazole Nitrate Microemulsion:
- Oxiconazole Nitrate: 0.30% - 3.00%
- Surfactant: 8.00% - 35.0%
- Cosurfactant: 4.00% - 25.0%
- Oil Phase: 5.00% - 10.0%
- Distilled Water: The remaining portion

The Oxiconazole Nitrate microemulsion has a mean diameter below 50nm, and the particle size distribution PDI is below 0.2.

For Blank Gel:
-Gel-type Vehicle: 3.00% - 8.00%
- Antiseptic: 0.50% - 2.00%
- pH Adjusting Agent: 4.00% - 13.0%
- Distilled Water: The remaining portion

VII. HOW TO USE OXICONAZOLE NITRATE CREAM

Instructions for Applying Medication on the Skin

1. *Location Preparation:*
   - Clean and thoroughly dry the area to be treated.
2. *Application Frequency:*
   - Apply this medication to the affected skin as directed by your doctor, usually once or twice a day.
3. *Dosage and Treatment Length:*
   - The dosage and length of treatment depend on the type of infection being treated.
   - Do not apply this medication more often than prescribed, as it won't speed up the healing process and may increase side effects.
4. *Application Technique:*
   - Apply enough cream or lotion to cover the affected area and some of the surrounding skin.
   - If using lotion, shake the bottle well before applying.
   - Use cotton balls or a soft cloth to apply the lotion.
5. *After Application:*
   - After applying this medication, wash your hands.
6. *Bandaging:*
- Do not wrap, cover, or bandage the area unless directed to do so by your doctor.
7. *Avoid Sensitive Areas:*
   - Do not apply this medication in the eyes, nose, mouth, or vagina.
8. *Consistency is Key:*
   - Use this medication regularly at the same time(s) each day to get the most benefit from it.

Side Effects

- *Common Side Effects:*
  - Burning
  - Stinging
  - Swelling
  - Irritation
  - Redness
  - Pimple-like bumps
  - Tenderness
  - Flaking of the treated skin

If any of these effects persist or worsen, it is advisable to promptly inform your doctor or pharmacist.

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Uses

Oxiconazole is an azole antifungal medication employed to combat skin infections, including athlete's foot, jock itch, ringworm, and a skin condition called pityriasis (tinea versicolor). Pityriasis can result in lightening or darkening of the skin on the neck, chest, arms, or legs. The primary mechanism of action for oxiconazole involves inhibiting fungal growth.

VIII. RESULTS

Formulation F5:

- Release Rate: 92.06% at 12 hours
- Skin Irritation: None observed
- Zone of Inhibition: Maximum when compared with the Oxiconazole nitrate marketed cream

IX. CONCLUSION

1. Formulation F5, an optimized emulgel, exhibited superior antifungal activity compared to a marketed formulation.[4]
2. The physicochemical properties of ON indicate its limited solubility in water, making it challenging to develop a water-soluble TGF based on poloxamer. Nevertheless, a TGF containing ON was successfully developed and subjected to characterization studies.
3. Characterization studies and time-dependent antifungal activity analysis confirmed that ON did not exhibit incompatibility with the formulation's adjuvants and maintained its effectiveness against C. albicans strain.[12]
4. OXZN-NLC has the potential to serve as an alternative for treating topical fungal infections pending clinical evaluation in the near future.[14]

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