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Original Research Article

# Development and Evaluation Topical Drug Delivery of Ketoconazole in the Treatment of Fungal Infection

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**Abstract**

**Background:** Fungal infections are prevalent and pose significant health risks, necessitating effective and targeted treatment options. Ketoconazole, a broad-spectrum antifungal agent, is commonly used in the treatment of various fungal infections. However, traditional formulations may have limitations in terms of drug release and patient compliance. Hydrogel-based drug delivery systems offer a promising alternative, providing controlled release, improved drug stability, and enhanced patient compliance.

**Objective:** This study aims to develop and evaluate a hydrogel-based topical drug delivery system for ketoconazole to improve its therapeutic efficacy in treating fungal infections.

**Methods:** Ketoconazole-loaded hydrogels were formulated using a combination of biocompatible polymers. Various formulations were prepared and characterized for their physicochemical properties, including pH, viscosity, and drug content. The in vitro release profile of ketoconazole from the hydrogels was evaluated using a Franz diffusion cell apparatus. Ex vivo skin permeation studies were conducted using excised human skin to assess the penetration capability of the hydrogel formulation. Additionally, antifungal activity was tested against common fungal strains to determine the therapeutic potential of the developed hydrogel.

**Results:** The prepared hydrogels exhibited satisfactory physicochemical properties with an optimal pH and viscosity suitable for topical application. In vitro release studies demonstrated a sustained release profile of ketoconazole over 24 hours. Ex vivo skin permeation studies indicated significant penetration of the drug through the skin layers, suggesting effective delivery to the target site. Antifungal activity tests confirmed the efficacy of the ketoconazole-loaded hydrogel against various fungal strains, with results comparable to conventional formulations.

**Conclusion:** The developed hydrogel-based topical drug delivery system for ketoconazole shows promising potential in enhancing the treatment of fungal infections. The sustained release, improved skin penetration, and effective antifungal activity indicate that this formulation could provide a better therapeutic outcome and increased patient compliance. Further in vivo studies and clinical evaluations are warranted to confirm these findings and explore the full potential of this novel drug delivery system.

**Keywords:** Hydrogel, Drug Delivery, Ketoconazole, Fungal Infection, Optimization, Candida Aspergillus Fumigatus.



## Introduction

Fungal infections are a significant global health concern, affecting millions of individuals and causing a range of conditions from superficial skin infections to systemic diseases. These infections can be particularly challenging to treat due to the resilience and adaptability of fungal pathogens. Ketoconazole, a widely used antifungal agent, has proven efficacy against various fungal infections, including those caused by dermatophytes, yeasts, and molds.

However, conventional formulations of ketoconazole, such as creams and ointments, often suffer from limitations in drug delivery efficiency, patient compliance, and stability. Topical drug delivery systems are advantageous for treating localized infections as they can deliver the drug directly to the site of infection, minimizing systemic side effects and enhancing therapeutic efficacy. Among the various topical delivery systems, hydrogels have gained significant attention due to their unique properties.

Hydrogels are three-dimensional polymeric networks capable of retaining large amounts of water or biological fluids, making them highly suitable for topical applications. They offer several benefits, including ease of application, good

biocompatibility, and the ability to provide controlled and sustained drug release.

The primary objective of this study is to develop and evaluate a hydrogel-based topical drug delivery system for ketoconazole. The rationale behind using a hydrogel matrix lies in its potential to overcome the limitations of conventional formulations. By incorporating ketoconazole into a hydrogel, we aim to achieve a formulation that provides sustained drug release, enhances skin penetration, and maintains the stability of the active ingredient.

This study involves the formulation of ketoconazole-loaded hydrogels using biocompatible polymers, followed by comprehensive characterization to assess their physicochemical properties. In vitro release studies and ex vivo skin permeation experiments are conducted to evaluate the release profile and penetration capability of the hydrogel formulation. Furthermore, antifungal activity tests are performed to confirm the therapeutic efficacy of the developed hydrogel against common fungal strains.

**Material and Method**

**Table 1: Hydrogel**

| Ingredients (mg) | H1 | H2 | H3 |
|---|---|---|---|
| ketoconazole | 200mg | 200mg | 200mg |
| Carbopol | 100mg | - | - |
| HPMC | - | 100mg | - |
| Guar Gum | - | - | 100mg |
| Propylene Glycol | 510mg | 510mg | 510mg |
| DMSO | 1ml | 1ml | 1ml |
| Methyl Paraben | 10mg | 10mg | 10mg |
| Propyl Paraben | 0.25mg | 0.25mg | 0.25mg |
| Water | 8.1ml | 8.1ml | 8.1ml |
| Total | ≈10gm | ≈10gm | ≈10gm |

All the ingredients, including the active medication (ketoconazole), were combined in accordance with the formula indicated in the above table. One milliliter of DMSO should be used to dissolve 200 mg of ketoconazole. Beaker-A was used to label the medication ethanol, water, and propylene glycol solution after it had been prepared. Add 100 mg of cabolpol, HPMC, and gum gum to solution A and mix constantly for two hours at a speed of 500 revolutions per minute. Propylene glycol, methyl paraben, and propyl paraben were added to it along with triethanolamine, and the temperature was kept at 25 degrees Celsius. Water was used to determine the final weight. Prior to carrying out the assessment test, each of the samples was given a period of twenty-four hours at room temperature to acclimate to the environment.

**Evaluation for Gel**

**Standard curve of ketoconazole**

When the ketoconazole was described in methanol, the solvent, its absorption spectra was determined with a Shimadzu UV Visible Spectrophotometer. The medication's λmax value was found to be 255.nm when it was scanned between 180 and 400 nm.

A standard curve for ketoconazole could be created by using a UV spectrophotometer to plot absorbance measurements at different dosages of the drug. The standard plot was made with the absorbance as the Y-axis and the concentration (measured in micrograms per milliliter) as the X-axis.

**Table 2: Absorbance Ketoconazole**

| Concentration | Absorbance (255nm) |
|---|---|
| 0.0 | 0 |
| 2.0 | 0.127±0.002 |
| 4.0 | 0.254±0.003 |
| 6.0 | 0.379±0.001 |
| 8.0 | 0.521±0.002 |
| 10.0 | 0.648±0.003 |
| 12.0 | 0.794±0.001 |

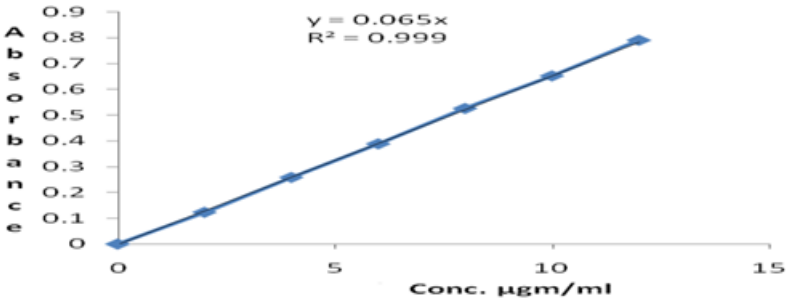


**Figure 1: Calibration Curve Ketoconazole**

**Percentage Yield**

The container that was empty was both the container in which the gel formulation was housed and the container itself were weighed, and then the gel formulation was weighed once again. After that, the practical yield was calculated by subtracting the weight of the empty container from the weight of the container containing the gel formulation. The formula was then used to determine the percentage of yield that was obtained

% Yield = Practical Yield / Theoretical Yield X 100

**API content**

Each gel formulation weighted ten grams in total, which were then added to a volumetric flask holding twenty milliliters of alcohol. Thirty minutes were spent swirling the mixture. It was filtered after 100 milliliters of liquid were added. The solution stated above was diluted with an additional 1 ml of alcohol until it reached a volume of 10 ml. This was followed by another 1 ml of alcohol dilution until the solution reached a volume of 10 ml.

Using spectrophotometric analytical techniques, the absorbance of the solution was measured at a wavelength of 415 nm for amphotericin-B and 255 nm for ketoconazole. This is the formula that was utilized to calculate the drug's concentration.

Drug Content = Absorbance / Slope X Dilution Factor X 1/1000

**Determination of pH**

Using a digital pH meter, the pH of each gel formulation was measured after 50 grams had been transferred into a beaker holding 10 milliliters. For best effects, the pH of the topical gel formulation used to treat skin infections should be between 3 and 9.

**Spreadability**

After a minute, the spreadability of the gel formulation was assessed by measuring the distance between two 20 cm × 20 cm horizontal plates from which a single gram of gel was spread. The standard weight that was secured to the top plate weighed 250 grams.

**Extrudability**

The gel compositions were kept in a metal tube made of aluminum or that could be folded up. The material was extruded by pushing the tube, and the formulation's Extrudability was confirmed.

**Viscosity estimation**

The technique kept in mind the variables that affect viscosity, such as temperature, pressure, and sample size, among others. The viscosities at various places along the path were obtained by adjusting the helipath T-bar spindle up and down. There was never a torque reading below 10%. The viscosity of gels was determined by taking an average of three readings in a minute.

**Pre-formulation Studies**

**Table 3:**

| S. .No. | Drug | Physical appearance | Melting point (°C) |
|---|---|---|---|
| 1. | Ketoconazole | White | 152°C |

**Table 4:**

| S. No. | Drug | Solubility | | | | |
|---|---|---|---|---|---|---|
| | | Dimethyl sulphoxide | Dimethyl formamide & Methanol | Benzene & Ethanol (95%), | Ether & Water | (DMSO) |
| 1. | Ketoconazole | (-) | (-) | (-) | (-) | (+++) |

**Analytical Profile of Active Drug (DSC & FTIR)**

a) **Ketoconazole:** Figure 2 displays the ketoconazole DSC thermogram. Ketoconazole's DSC thermogram revealed a strong peak at 1620C. By comparing a compound's identification to that of a genuine sample, one can verify the presence of functional groups in an unknown molecule using infrared spectra. The acquired infrared spectra were explained for significant groupings of chromophores. The IR spectra showed peaks at 3640, 1450, 1057, 1250, 810 and 690 $cm^{-1}$.

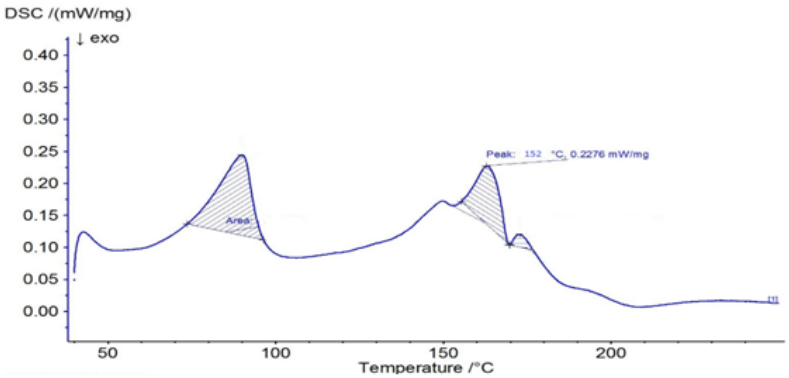


**Figure 2: DSC Thermogram of Ketoconazole**

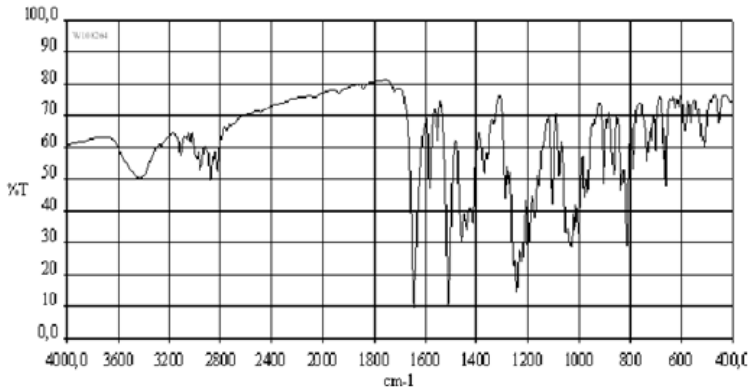


**Figure 3: IR Spectra of Ketoconazole**

**Table 5: FTIR Spectra of Ketoconazole**

| Functional Group | Observed Value ($cm^{-1}$) |
|---|---|
| C-Cstretch | 1579 |
| C-Nstretch | 1429 |
| $CH_2$ stretch | 2585 |
| CH stretch | 2954 |
| C-Nstretching | 3150 |

**b) DSC of Ketoconazole and various polymers (Compatibility Study)**

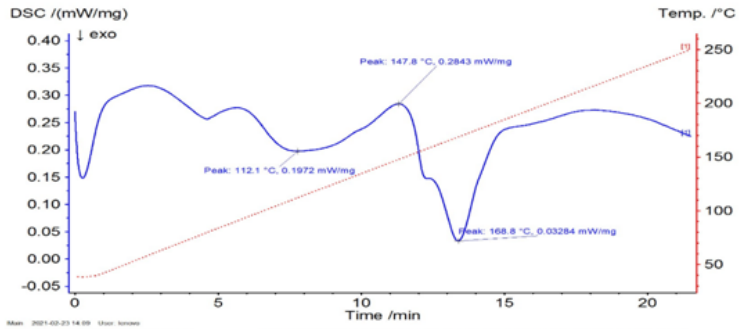


**Figure 4: DSC Carbopol + Coconut oil + arcachis oil + Ketoconazole**

**Physical Evaluations**

**a) pH**

pH of prepared formulation was evaluated by Digital pH meter. The pH of prepared formulations observed in range 6.5to 7.2.

**b) Viscosity measurements**

The Helipath T- Bar spindles were rotated up and down in the sample giving variable viscosities at a number of points programmed over the time. The readings taken over a period of 60 seconds at 6.5 to 10 rpm were averaged to obtain viscosity.

**Extrudability**

The extrudability of the gel formulations were checked as per the procedure. Extrudability of carbopol and HPMC gels were excellent than Guar gum gel.

**Determination of Spreadability**

The Spreadability of gels was determined as per the procedure. From Spreadability data is observed that the formulation with carbopol-934 showed maximum (8cm), where as the formulations with carbopol-940, HPMC and Guar gum were showed significant Spreadability.

**Scanning and Determination of Maximum Wavelength ($\lambda_{MAX}$)**

**Table 5: Scanning of Ketoconazole in different solvents**

| S. No. | Solvent Used | Concentration of final aliquots solution (10 µg/ml) | |
|---|---|---|---|
| | | $\lambda_{max}$ | Absorbance |
| 1. | DMSO | 255 | 0.671 |
| 2. | Ethanol | 255 | 0.629 |
| 3. | Methanol | 255 | 0.717 |
| 5. | Phosphate Buffer (pH 6.8) | 255 | 0.631 |

**In-Vitro Release**

**a) Ketoconazole**

**Table 6: H1 In-Vitro Release**

| Time (minutes) | Absorbance at 255nm | Concentration (µg/ml) | Amount of drug release (mg) | Percentage drug release* |
|---|---|---|---|---|
| 30 | 0.184 | 10.03 | 1.803 | 18.03 |
| 60 | 0.364 | 15.698 | 2.939 | 29.39 |
| 90 | 0.48 | 28.311 | 5.417 | 54.17 |
| 120 | 0.521 | 34.789 | 6.777 | 67.77 |
| 150 | 0.619 | 36.758 | 7.576 | 75.76 |
| 180 | 0.668 | 41.095 | 8.019 | 80.19 |

**Conclusion**

A promising strategy for treating fungal infections is the use of hydrogel-based topical drug delivery devices, which provide increased efficacy, better patient compliance, and decreased systemic toxicity. Hydrogel formulations containing ketoconazole have great potential to meet unmet requirements in current antifungal therapy through design, development, and optimization.

This study's findings suggested that formulation H1, containing 1% carbopol-934, would be the most effective one due to its strong in vitro release profile, stability, and bioavailability. Pharmacokinetic information may be necessary for the dose form's continued usefulness, according to the study's findings. Antifungal activity research in the future could be helpful in this difficult field.

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