Acta Scientific Pharmaceutical Sciences

Volume 2 Issue 6 June 2018

Research Article

Antifungal Gel of Miconazole Nitrate: A Comparative Effect Study with Accumulation of Antioxidants and Surfactants

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Received: March 26, 2018; **Published**: May 21, 2018

Abstract

Miconazole nitrate is widely used as an antifungal drug with a poor aqueous solubility, which requires the development of new delivery systems to improve its therapeutic activity. Fungal infections are caused by the microscopic organisms that invade the epithelial tissue. However, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) are known as potent antioxidants with antimicrobial properties. In an attempt to develop a better formulation with an antifungal profile, a surfactant aided micellar system was dispersed within miconazole nitrate gel formulation. In the proposed study, the prepared gel was evaluated for its physiochemical properties, *in vitro* drug release profile. It can be concluded that the addition of antioxidants and surfactants gives more promised effect in the release of miconazole nitrate.

Keywords: Antioxidants; Micellar System; Miconazole Nitrate; Topical Gel; Antifungal Activity

Abbreviations

BHA: Butylated Hydroxyanisole; BHT: Butylated Hydroxytoluene; USP: United States Pharmacopeia; SDS: Sodium Dodecyl Sulfate; CMC: Critical Micelle Concentration; EtOH: Ethanol; TEA: Triethanolamine

Introduction

Fungal infection of skin is now-a-days one of the most common dermatological problems. Infection is caused by microscopic organisms that invade the epithelial tissue. The fungi kingdom includes yeasts, moulds, rusts and mushrooms which are commonly found on the skin, mouth, throat, stomach, colon, rectum and vagina. Whenever proliferation of this kind of organism occurs, it can produce symptomatic infection of the skin, mouth, vagina and intestine [1]. The incidences of mycoses especially superficial fungal infections are increasing and covers more than 25% of the world's population. It is found that disease progression is very rapid, and severity increases in patients with compromised immune function [2].

The physicians have a wide choice of treatment from solid dosage to semi solid dosage form and liquid dosage formulations. Among the topical formulations, topical gels are widely accepted in both cosmetics and pharmaceuticals. Gels are semisolid dosage form in which the liquid phase is constrained within the three-dimensional polymeric matrices in which high degree of physical cross-linking has been introduced. The USP defines a semi solid system consisting of dispersion made up of either small inorganic particles or large organic molecules enclosing or interpenetrated by liquid. Gels are generally made with the help of suitable gelling agents. Gels are often non-greasy and are generally applied externally [3].

Miconazole nitrate is an antifungal drug which is used for the formulation and is available commercially as tablets and injections in spite of its well-known adverse effects including nausea, vomiting, bloating and abdominal discomfort. In order to bypass these disadvantages, the gel formulation has been proposed as topical application.

Materials and Methods

Materials

Miconazole Nitrate was obtained from Yarrow Chem Products, Mumbai, India. Carbopol 940, Butylated Hydroxy Anisole (BHA), Butylated Hydroxy Toluene (BHT), Sodium Dodecyl Sulfate (SDS) and Triton X- 100 were obtained from Loba Chemicals Ltd. Mumbai, India. Triethyl amine, Sodium Hydroxide and n-octanol were procured from Merck India Limited, Mumbai, India. All other materials used were of analytical grade.

Method of preparation of gel

Preparation of micellar solution with SDS and TX100

Two optimized surfactants (SDS and TX100) of concentration near/above CMC's were selected. Likely for SDS (6.0, 7.0 and 8.0 mmolkg-1) and TX100 (0.20, 0.22, and 0.24 mmolkg-1) were the selected concentrations. Optimized concentrations were selected

for BHA and BHT with respect to obtained CMC's values of surfactants in 30% v/v EtOH. All the calculated concentrations based on the thermophysical analysis are presented in table 1. Accordingly, BHA and BHT were added to the surfactant hydroethanolic solutions (30% v/v EtOH) and then mixture was mixed using sonicator for 10 minutes. This step is followed by filtration of the mixture. The prepared micellar solution was dispersed into the gel.

S. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7
	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)
1	Drug (Miconazole Nitrate)	5	5	5	5	5	5	5
2	BHA	-	5	-	5	-	2.5	2.5
3	BHT	-	-	5	-	5	2.5	2.5
4	SDS	-	5	5	-	-	5	-
5	TX-100	-	-	-	5	5	-	5

Table 1: Different Gel Formulations.

Preparation of gel library

The gel base was prepared by dispersing the carbopol 940 (Polymer) in distilled water. Carbopol 940 was chosen due to its hydrophilic nature and bio adhesive property, which might result in an increased residence time of the compound at the site of absorption when comes in contact with the topical membrane. The polymer was weighed accordingly for each formulation and then soaked in distilled water for 2 hours prior to use. To obtain a homogenous gel base, it was subsequently dispersed in distilled water using magnetic stirring for 1h. This step is followed by addition of SDS/TX100 immobilized BHA, BHT and BHA + BHT to the gel base. At last, Triethanolamine (TEA) was added drop wise to obtain neutralize carbopol gels and was subjected to constant stirring [4].

Characterization

Homogeneity: All developed gels were tested for homogeneity by visual inspection. They were tested for their appearance and presence of any aggregates.

Grittiness: All the formulations were evaluated microscopically for the presence of particles if any. No appreciable particulate matter was seen under the light microscope. Here, obviously the gel preparation fulfils the requirement of freedom from particulate matter and from grittiness as desired for any topical preparation.

Extrudability Study: The extrudability of formulations from aluminium collapsible tubes were determined by filling the tube with gel preparation and then by applying weight on the tube the extrudability was checked [5,6].

All these Physicochemical Characters of Gels Formulations are shown in table 2.

Measurement of pH: The pH of formulation was determined by using pH meter. 1g of gel was dissolved in 100 ml of distilled water and stored for 2 hours. The measurements of pH of formulations were done in triplicate and standard deviation was calculated. pH of the gel must be ideally near to normal pH of the skin to avoid irritation [7].

Formulation	Homogeneity	Grittiness	Extrudability
F1	+++	-	Pass
F2	++	-	Pass
F3	++	-	Pass
F4	+++	-	Pass
F5	+++	-	Pass
F6	++	-	Pass
F7	+++	-	Pass

Table 2: Physicochemical Characters of Gels Formulations.

Viscosity Study: The measurement of viscosity of the prepared gel was done with a Brookfield viscometer. The gels were rotated at 20 rpm and 50 rpm using spindle no. 64; the corresponding dial readings were noted [7].

Spreadability: Spreadability is expressed in terms of time that two slides take to slip off from the gel and placed in between the slides under the direction of certain loads, lesser the time taken for separation of two slides, better the spreadability [7].

$$S = M \times L/T$$

Where, M = Weight tied to upper slide
L = Length of glass slide
T = Time taken to separate the slides

Drug Content: 1g of gel was taken and dissolved in 100 ml of methanol. The volumetric flask was kept for 2 hours and shaken well to mix it properly. The solution was passed through the filter paper and filtered 1 ml of above solution was taken and diluted to 10 ml in 10 ml volumetric cylinder, this solution was measured spectrophotometrically at 273 nm [8,9].

Physiological Evaluation Data of Gel Formulations are presented in table 3.

***In vitro* Permeation Studies:** The *in vitro* diffusion studies of prepared gel were carried out using Keshary-Chien diffusion cell. The diffusion study was performed using 500 mg of gel containing 2.5 mg of Miconazole Nitrate. Gel was spread uniformly on the cellophane membrane. In Keshary-Chien diffusion cell 6 ml of

phosphate buffer was used as receptor compartment. The donor compartment was kept in contact with the receptor compartment, and the temperature was maintained at 37 ± 0.5°C. The solution on the receptor side was stirred by externally driven Teflon coated magnetic stirrer using a small bead. The sample of 2 ml was withdrawn at different time intervals and replacement was done with 2 ml of fresh buffer. The drug concentration on the receptor fluid was determined spectrophotometrically against blank [7].

Data Analysis

The cumulative amount of Miconazole Nitrate permeated expressed in percent was plotted for all formulations are shown as in figure 1. The cumulative amount of drug permeated of cellophane membrane at the end of 7h was compared

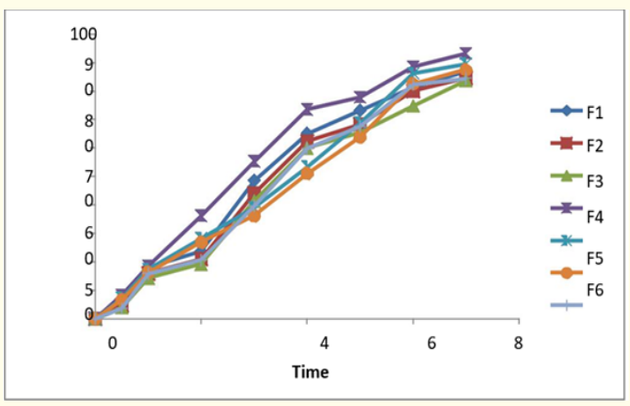

Figure 1: Zero Order Release Cumulative % Drug Released Vs. Time (h) of F1- F7.

In vitro Release Studies of Formulated Gel using Franz Diffusion Cell.

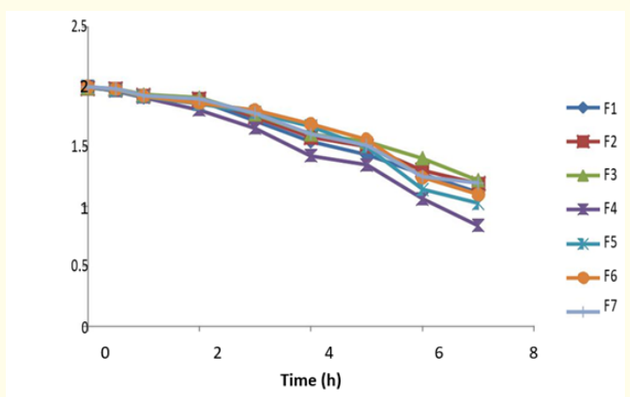

Figure 2: First Order Release Log % Drug Remaining Vs. Time (h) of F1 to F7.

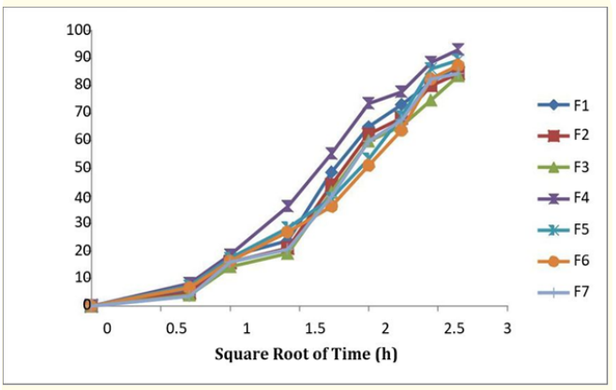

Figure 3: Higuchi Release Cumulative % Drug Release Vs Square root of Time of F1 to F7.

From the above results, it is clear that formulation F4 is the best formulation and it was taken for stability study.

Stability study

Stability is essential factor of quality, safety and efficacy of drug product. A drug product, which is not of a sufficient stability, can result in changes in physical as well as in chemical characteristics [9].

Protocol for Stability Studies of Gel Formulation [10-14]

Purpose

To evaluate the stability profile of drug product (topical gel formulation F4) for storage under refrigerated, real time and accelerated conditions.

Test design

The product was properly filled in collapsible tubes and was stored according to storage conditions.

Testing plan

Topical gel formulation F4 was filled in the collapsible tubes and was stored at the following storage conditions.

Testing and Test Criteria

The sample was stored and tested in accordance with storage condition and valid test method. The sample was taken out of storage on planned testing date (Table 4). The parameters to be tested were follows:

- Physical Test-appearance (P.A)
- Drug Content (D.C)

Stability studies are shown in table 4 and results related to that are shown in figure 4.

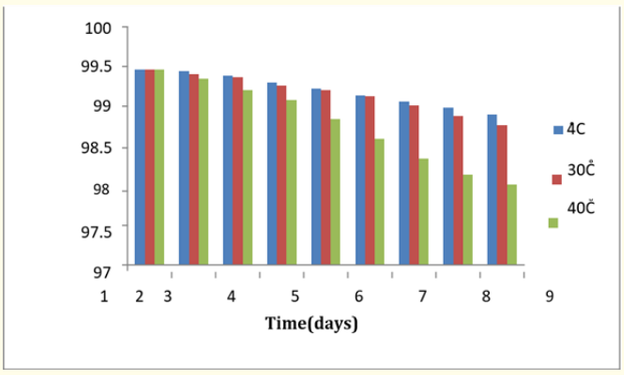

Figure 4: Stability Profile of Formulation F4.

Result and Discussion

In the present research work an attempt was made to develop and characterize the antifungal gel of Miconazole Nitrate using Carbopol 940 for the treatment of fungal infections. Gels are semi-solid dosage form in which the liquid phase is constrained within the three-dimensional polymeric matrices in which high degree of physical cross-linking has been introduced. They were made with the aid of suitable gelling agent.

Different gel formulations were prepared based on thermo-physical analysis. All the formulations were investigated for homogeneity, grittiness, extrudability, pH, viscosity, spreadability, *in-vitro* permeation and stability studies. All gel formulations were elegant in appearance. A thin and smooth film was formed on application to the skin and easily washable with the water. The pH of all formulations lies between 7.2 to 7.5 which lie in the normal pH range of the skin. The viscosity of all formulations lies in between 23560 ± 20 to 36910 ± 30 Cps for formulations F1-F7 at 20 rpm and at 50 rpm viscosity lies in between 20746 + 21 to 35241 ± 20 cps. The results for spreadability lie between 10.53 ± 0.13 g.cm/sec to 14.21 ± 0.13 g.cm/sec for formulations F1-F7. The drug content for F1-F7 formulations lies between 86 ± 0.28 to 99.90 ± 0.28.

In *in-vitro* permeation study of drug, the maximum cumulative percent drug release was obtained at 8 hours which was 55% to 80% for formulations F1 to F7. To analyse the *in vitro* release data various kinetic models were used to describe the release kinetics which were zero order, first order and higuchi plot. The best kinetic model which described the release of drug is higuchi model which states the release from insoluble matrix as a square root of time dependant process based on fickian diffusion model.

The stability profile of drug product (topical gel formulation F4) for storage under Refrigerated (4°C/75% RH), Real Time (30°C/75% RH) and Accelerated (40°C/75%RH) conditions were performed at different sampling intervals such as 7, 14, 21, 28, 35, 42, 49, 60 days. The sample was tested in accordance with various parameters such as Physical Test Appearance (P.A) and Drug Content (D.C). No significant variation in the physical parameters (like gel leakage, colour and consistency) after 7 weeks at different stress conditions.

Conclusion

The highest release rate was found in formulation F4 which is having drug (Miconazole Nitrate (5mg)) and excipients BHA (5 mg) and TX-100 (5 mg). In stability studies, the formulation showed no significant variations and found to be stable. From the above results, it is clear that the combination of BHA and TX-100 showed promising results.

Conflict of Interest

The authors confirm that this article content has no conflicts of interest.

Acknowledgment

Some of the authors acknowledge Manav Bharti University Solan for the support and opportunity provided to them.

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