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Research Article

DESIGN, DEVELOPMENT AND EVALUATION OF FLUCONAZOLE TOPICAL GEL

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ABSTRACT

Objective: The present study was designed to formulate and evaluate Fluconazole topical gel.

Methods: The gel was formulated by using polymer sodium carboxy methyl cellulose in different ratio. The drug-excipient compatibility studies were confirmed by differential scanning calorimetry analysis. The evaluation of formulated fluconazole topical gel was carried out for physical appearance, pH-value, spreadability, rheological behavior, drug content and *in-vitro* release study.

Results: The rheological behavior of the prepared gels showed a pseudo plastic flow, which is a good characteristic of topical pharmaceutical gels. The formulated gel showed good physical characteristic and release profile. The release data was fitted into different kinetics equation**s** by regression analysis. Stability studies showed no significant change in physical appearance, rheological properties and drug release upon storage for 3 months at ambient condition.

Conclusion: Fluconazole was successfully incorporated into the different topical gel formulations, and the developed formula could be very promising topical alternative for the treatment of skin fungal infection.

Keywords: Fluconazole, Differential scanning calorimetry, Sodium carboxymethyl cellulose, Gel, Kinetic.

INTRODUCTION

Topical delivery is an attractive route for local and systemic treatment**s**. The delivery of drugs onto the skin is recognized as an effective means of therapy for local dermatologic diseases. Drug may penetrate deeper into the skin and hence give better absorption. Topical application has many advantages over the conventional dosage forms. Topical preparation avoids the GI-irritation, prevent the metabolism of the drug in the liver and increase the bioavailability of the drug. Topical preparations give its action directly at the site of action [1].

A gel is a two-component, cross linked three-dimensional network consisting of structural materials interspersed by an adequate, but proportionally large amount of liquid to form an infinite rigid network structure, which immobilizes the liquid continuous phase within. A gel is an intermediate state of matter possessing property of a solid and liquid, termed as viscoelasticity [2]. The structural materials that form the gel network can be composed of inorganic particles or organic macromolecules, primarily polymers [3].

Fluconazole is a newer water soluble triazole having a wider range of activity. It can cure vaginal candidiasis, tinea infection, cutaneous candidiasis, coccidioidal meningitis, fungal keratitis and other systemic fungal infections [4].

Fluconazole is available commercially as tablet, capsule, injection and eye drop formulations. The tablet and capsule dosage forms have well known side effects including nausea, headache, abdominal pain, vomiting and diarrhea. In order to bypass these disadvantages, the gel formulation has been proposed for topical applications. The goal of this research work was to formulate an effective, stable topical gel containing fluconazole with desired *in-vitro* performances. Finally, release data were fitted with different kinetic equations to establish the drug release mechanism from the gel matrix.

MATERIALS AND METHODS

Materials

Fluconazole (Gifted by Drakt international Pvt. Ltd., Vadodara, Gujrat), Sodium Carboxy Methyl Cellulose (Loba Chemie Pvt. Ltd., Mumbai), Methyl Paraben (Merck Limited, Mumbai), Propylene Glycol, Glycerol (New Bengal Drug House, Kolkata) were used without further purification. All the other chemicals were of analytical grade. Dialysis Membrane was procured from Hi Media Laboratories Pvt. Ltd., Mumbai (Avg. flat width 39.41 mm and avg. diameter 23.8 mm).

Methods

Preparation of the fluconazole gel

Fluconazole gel**s** of different drug-polymer ratio (1:1, 2, 3, 4, 5, and 6) were prepared by following method. Polymer sodium carboxymethyl cellulose (NaCMC) of defined quantity was mixed with distilled water and stirred with a magnetic stirrer properly until they were mixed completely. Drug fluconazole was mixed homogeneously with glycerin and propylene glycol. The drug mixture was added to the polymer mixture. Then preservative (methyl paraben) was dissolved in alcohol and then added to the drug-polymer mixture and stir properly. Finally, prepared homogeneous formulation was freezed overnight in order to obtain a clear transparent gel [5].

Evaluation of the fluconazole gel

Physical evaluation [6]

Physical appearance such as color and overall appearance were checked under normal day light.

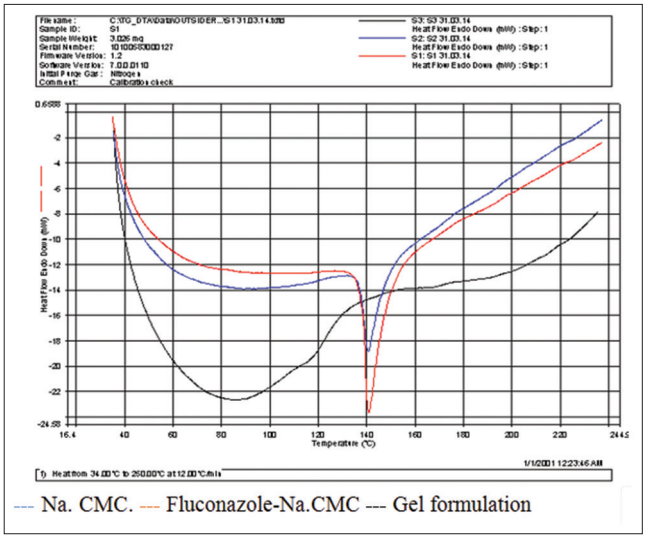
Drug-excipients compatibility studies [7]

Differential scanning calorimetry (DSC)

DSC studies were performed for the polymer (NaCMC), drug (fluconazole) and the drug-polymer physical mixtures in the ratio 1:1. The samples (3-4 mg) were taken in aluminium pans and heated at the rate of 10°C/minutes, to a temperature of 200°C using a differential scanning calorimeter (Pyris Diamond TG/DTA, PerkinElmer, Singapore) in nitrogen atmosphere (150 ml/minutes). Platinum crucible was used with alpha alumina powder as reference (Fig. 1).

Measurement of pH [6]

The pH of all gel formulations were determined by dipping pH-electrode of a digital pH meter in the gel formulations.



--- Na. CMC. --- Fluconazole-Na.CMC --- Gel formulation

Fig. 1: Differential scanning calorimetry study of polymer sodium carboxymethyl cellulose (NaCMC), fluconazole-NaCMC, gel formulation

Spreadability [8]

Required quantity of gel formulation was placed in between two glass slides of specific length. The upper slide was fitted with a string that was tied with a fixed weight. The string was passed over a pulley, and the weight was hung from the string. Under the weight, the upper glass slide took time to slip off. The time was noted. Lesser the time is taken for separation of two slides, better the spreadability.

Spreadability is calculated by using the formula: S = M. L/T

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

Viscosity study [9]

The viscosities of the prepared gel formulations were determined at 25°C using Brookfield viscometer (model DV-I+, Brookfield Engineering Laboratory, INC., USA.). The spindle (T-D) was rotated at specific rpm. The viscosities of the formulations were more correct when it was near to 100% torque.

Drug content determination [9]

A specific quantity of developed gel was taken and dissolved in 50 ml of phosphate buffer of pH 7.4. The volumetric flask containing gel solution was shaken for 2 hr on the mechanical shaker in order to get complete solubility of the drug. This solution was filtered using Millipore filter (0.45 µm). Drug absorbance was recorded by using UV-Visible spectrophotometer at $_{\lambda max}$ 266 nm using phosphate buffer (pH 7.4) as blank.

***In vitro* release studies [10]**

The study was carried out using dialysis membrane. One gram of the fluconazole gel was placed on a circular aluminum foil. The foil was placed on the dialysis membrane and pressed to spread uniformly in order to get a uniform thickness of the gel throughout the foil. The membrane was tied with the open end of a test tube such that the gel remained in the donor side of the membrane placed on a test-tube of defined diameter. The test-tube was then immersed in the vessel containing 100 ml of the release medium, phosphate buffer pH 7.4 maintained at 37°C±0.5°C in a precision water bath. The membrane just touched the release medium at the receptor side. Aliquots (5 ml) volumes of samples were withdrawn at every 30 minutes over 2 hr and 30 minutes and were immediately replaced with fresh medium pre-warmed to 37°C±0.5°C. The samples were assayed in a UV spectrophotometer at λ_{max}=266 nm and the concentration of the drug was determined by using the equation of the standard curve.

Drug release kinetic study [11]

The data obtained from the *in vitro* release study were analyzed using linear regression method according to the following equations:

i. Zero order
   $Qt=K_0t$
   Where, Q= Amount of drug release in time t
   K_0 = Zero order rate constant expressed in unit of concentration/time
   t = Release time
ii. First Order
   $\text{Log } Q=\text{Log } Q_0-kt/2.303$
   Where, Q_0= is the initial concentration of drug, k= is the first order rate constant,
   t = release time
iii. Higuchi model
   $Q=kt1/2$
   Where, k= Release rate constant, t = release time
iv. Hixson-Crowell model

$$W_0^{1/3}-W_t^{1/3}=kt$$

Where, W_0 = initial amount of drug in the pharmaceutical dosage form, W_t = remaining amount of drug in the pharmaceutical dosage form at time *t* and κ = rate constant incorporating the surface volume relation

v. Korsmeyer-Peppas model

$Mt/M\infty = Kt^n$

Where, Mt = amount of drug released at time t

M∞ = amount of drug released after infinite time

Mt/M∞ = fraction solute release

t = release time, K = kinetic constant incorporating structural and geometric characteristics of the polymer system, n = diffusion exponent that characterizes the mechanism of the release of traces.

The results are shown in Table 1 and Figs. 2-6.

Stability study [9]

The stability study was performed as per ICH guidelines. The formulated gel were filled in the collapsible tubes and stored at different temperatures and humidity conditions for a period of 3 months.

RESULTS AND DISCUSSION

The pre-formulation study of drug-excipients interaction was carried out by DSC, which showed no interactions. All the prepared formulations were white in colors, transparent and homogeneous. The formulations showed pH range 6.78-7.10 and drug content range 98.29-99.92%. The spreadability ranges of all formulations are 6.25-8.45 (Table 2).

The viscosity ranges of all formulations are 1030-1247 centipoises. The viscosity increases upon increasing the polymer concentration. The gel prepared with Sodium CMC exhibits pseudo-plastic flow. The viscosity of these gels decreases with increasing rate of shear, with no yield value. As the shearing stress is increased, the disarranged molecules begin to align their long axis in the direction of flow with release of solvent from the gel matrix [2].

The percent of Fluconazole release over a period of 2 hrs 30 minutes from the prepared gel formulations containing the same initial drug concentration (1% w/w Fluconazole) are discussed based on using different polymer concentration. The percent of fluconazole release

from the prepared NaCMC gel decreases significantly as the polymer concentration increases. The F1 batch shows better release profile than other (Fig. 7). The results of the *in-vitro* release study verified that the concentration of polymer had a remarkable influence on the drug releasing from the *in situ* gels [12]. Studies showed that drug release was decreased with an increase in gelling agent concentration because polymer concentration increases, as well as viscosity increases [6].

The release data analysis was carried out using various kinetic model like zero order, the first order, Higuchi model, Hixon–crowell model and Korsmeyer–peppas model, which shown in Figs. 2-6. [11]. The R^2 value

Table 1: Kinetic study of the *in-vitro* release data of prepared fluconazole gel

Formulation code	Zero order	First order	Higuchi model	Hixon crowell	Korsmeyer model
	Correlation coefficient (R^2)				
F1	0.8049	0.8202	0.9740	0.5731	0.5335
F2	0.9110	0.9560	0.9932	0.7571	0.6255
F3	0.9450	0.9410	0.9920	0.6781	0.5953
F4	0.8558	0.8613	0.9915	0.6059	0.5815
F5	0.9364	0.9439	0.9934	0.6732	0.7068
F6	0.9385	0.9447	0.9851	0.6910	0.7038

Table 2: Physical properties of prepared fluconazole topical gel

Formulation Code	Color	Spreadability (cm)	pH	Drug content	Viscosity (cps)
F1	White	8.45	7.02	99.92±0.82	1030
F2	White	8.18	6.78	99.47±0.67	1068
F3	White	7.50	7.00	99.12±0.24	1124
F4	White	7.28	6.91	99.37±0.52	1156
F5	White	6.87	6.87	98.29±0.91	1216
F6	White	6.25	7.10	98.64±0.72	1247

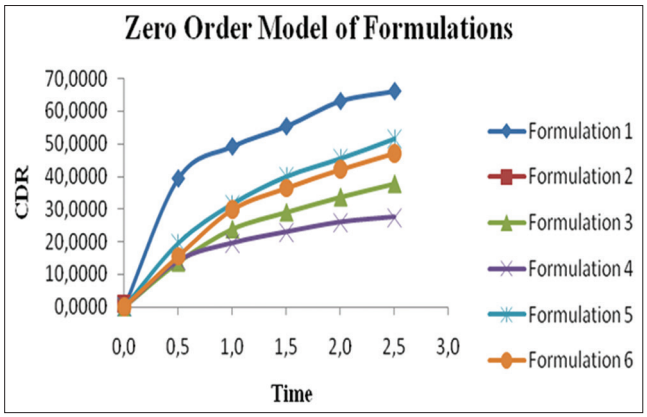


Fig. 2: Zero order release plot for prepared gel formulations

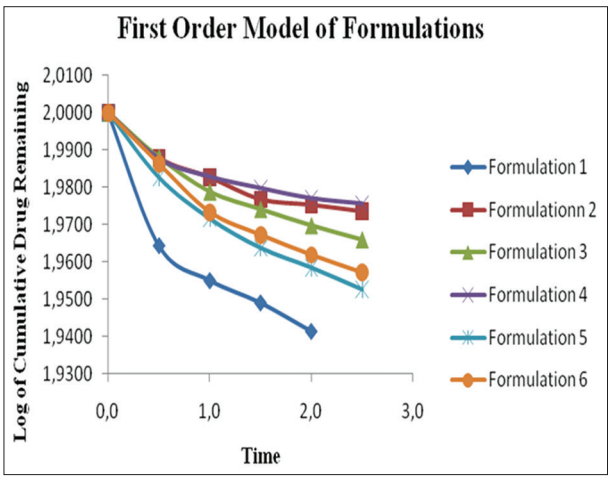


Fig. 3: First order release plot for prepared gel formulations

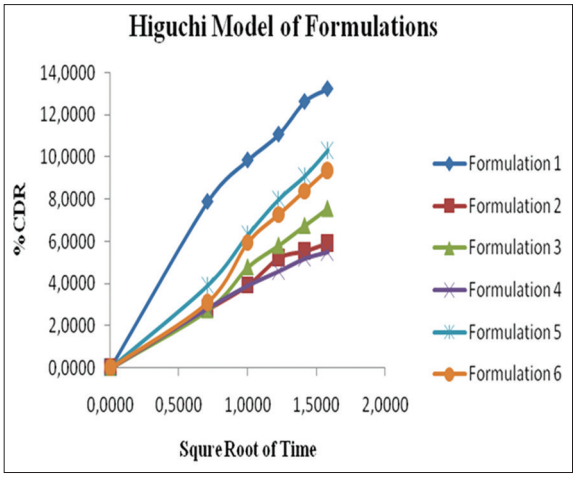


Fig. 4: Higuchi release plot for prepared gel formulations

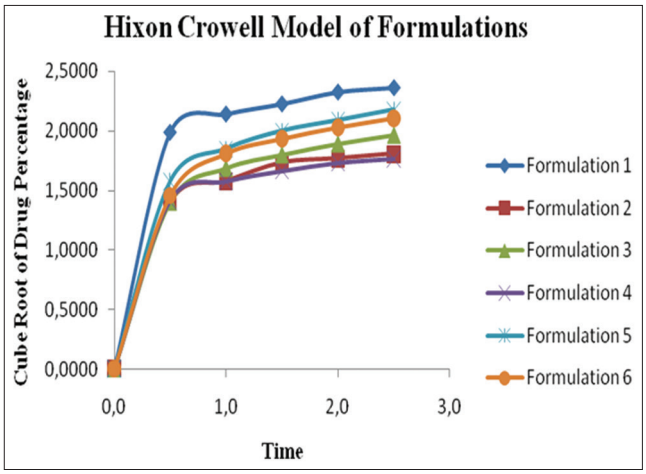


Fig. 5: Hixon crowell release plot for prepared gel formulations

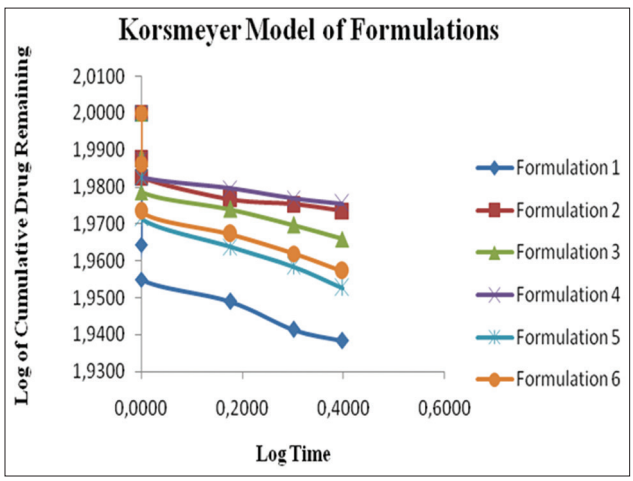


Fig. 6: Korsmeyer release plot for prepared gel formulations

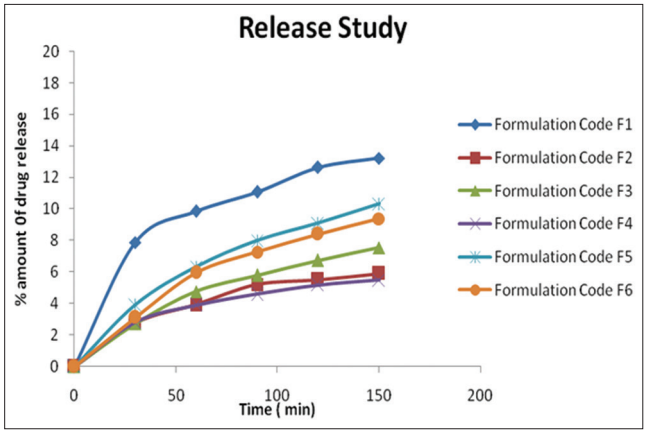


Fig. 7: Release profile of prepared fluconazole gel formulations

was tabulated in Table 1. The all above formulation was best fitted with Higuchi model.

After stability study, there were not much more variation at physical parameter and release pattern in all above prepared fluconazole gel formulations.

CONCLUSION

From the experiment, it is concluded that Fluconazole was successfully incorporated into the different topical gel formulations. F1 showed good pH value, spreadability, viscosity and highest *in-vitro* release profile after 2½ hrs among all the prepared different formulations. Therefore, it was concluded that our formula could be very promising topical alternative for the treatment of skin fungal infection. However, further preclinical, clinical and long-term stability studies should be required.

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