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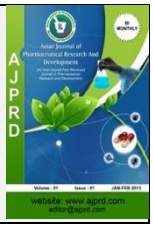

Open Access Research Article

Formulation and Evaluation of Fluconazole Gel for Topical Application

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A B S T R A C T

Objective: The development of topical gel formulation is needed because it offers an interesting alternative for oral route to achieving systemic and local effect of drug. Topical gel is having important advantages like avoid GI irritation, avoid first pass metabolism and increase the bioavailability of the drug. Fluconazole is a synthetic triazole antifungal drug used in the treatment and prevention of superficial and systemic fungal infection. Adverse effects reported with fluconazole most commonly affect the gastrointestinal tract and include abdominal pain, diarrhoea, flatulence, nausea and vomiting, and taste disturbance after oral administration. In order to bypass these disadvantages, the gel formulations have been proposed as topical application.

Method: Topical gel was prepared using combination of Carbopol and guar gum. Evaluation of the topical gel of fluconazole was carried out for physical appearance, pH, Spreadability, Extrudability, Rheological studies, Drug content, antifungal activity, in vitro release, Ex- vivo permeation study and skin irritation study.

Result: The varying concentrations of two polymers were found to affect the gel parameters like drug release, Spreadability and its viscosity. The accelerated stability studies were performed according to ICH guidelines for 3 months and the results were found to be stable in varying temperature.

Keywords: Fluconazole, hydrogels, rheology, in vitro release, kinetics, antifungal activity.

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INTRODUCTION:

Topical drug delivery is an attractive route for local and systemic treatment.[1]Fluconazole is a triazole derivative, used to treat fungal infection. It is used in the treatment of esophageal, oropharyngeal, or vulvovaginal candidiasis as well as other serious systemic candida infections. It is also effective against superficial fungal infections and dermatophytoses.[2]Adverse effects reported with fluconazole most commonly affect the gastrointestinal tract and include abdominal pain, diarrhoea, nausea and vomiting, and taste disturbance after oral administration. In order to bypass these disadvantages, the topical gel formulations have been proposed as topical application.

Topical preparations are applied directly to an external body surface by spreading, rubbing, spraying or instillation. Formulations applied on skin such product referred as topicals or dermatologicals.[3]Drugs are applied topically that is to the skin, mainly for local action.[4]Topical treatment of dermatological disease as well as skin care, a various formulation ranging from solids to semisolids and liquids preparations is available to clinicians and patients. The use of transparent gels from semisolid group has expanded both in cosmetics and in pharmaceutical preparation.[5]

MATERIALS AND METHODS

Materials

Fluconazole was received from Glenmark pharmaceutical Ltd. Carbopol 934P (loba chemicals Mumbai), Methyl paraben, propyl paraben, triethanolamine and propylene glycol was purchased from the loba chem industries.

Method

Accurately weighed quantities of polymers were dispersed in a small quantity of distilled water to form a homogeneous dispersion. Then in another beaker dissolve accurately weighed quantity of drug in propylene glycol and then added to the above solution. Methyl paraben and propyl paraben were dissolve in small quantity of water and added to above mixture with continuous stirring. The final weight of the topicalgel was adjusted with distilled water. The pH of the gels was adjusted to skin pH. The gels were stored in wide mouthed bottles.

Table 1: Composition of Topical gel formulations

Ingredients (%)	F1	F2	F3	F4
Fluconazole	0.5	0.5	0.5	0.5
Guar gum	-	0.1	0.2	0.3
Carbopol 934	0.5	0.5	0.5	0.5
Methyl paraben	0.1	0.1	0.1	0.1
Propyl paraben	0.05	0.05	0.05	0.05
Propylene glycol	20	20	20	20
TEA	q.s.	q.s.	q.s.	q.s.
Water (upto)	100	100	100	100

Fourier Transform Infrared (FT-IR) Studies

FTIR spectra of pure Fluconazole and gelling agents as shown Figure 1-2 were taken to assurethe compatibility. Infrared spectrum was taken (Shimadzu) by scanning the samples in KBr discs.

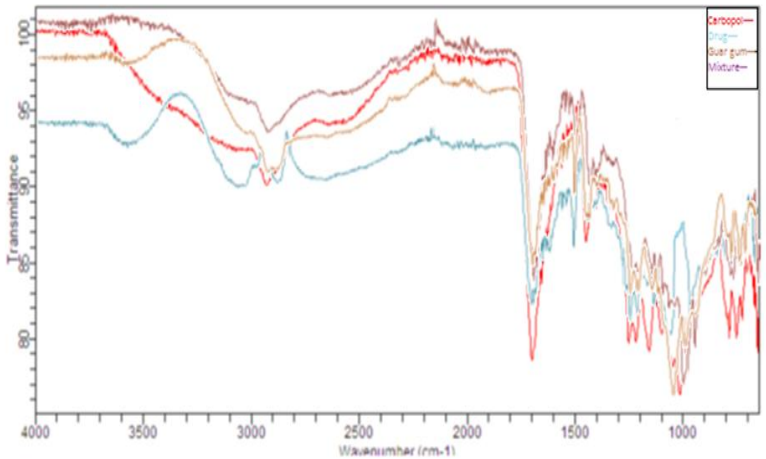

Figure 1: Fourier Transform Infra-red overlay of drug, polymers (Carbopol 934 and Guar gum) and mixture

EVALUATION PARAMETERS [6-17]

pH

The pH of gel formulations was determined by with the help of digital pH meter.

Clarity

Clarity of various formulation was determined by visual inspection under black and white backgroundand it was graded as follows: turbid +; clear ++; very clear (glassy) +++.

Homogeneity:

After the gels had been set in the container, all of the generated gels were visually inspected for homogeneity.They were examined for their appearance and presence of any aggregates.

Drug content

The drug content was evaluated by dissolving 1 g of the formulation correctly weighed in phosphate buffer pH 7.4 using a magnetic stirrer to get complete solubility.Then, the mixture was quantitatively transferred into volumetric flask 25 ml and completed to mark with phosphate buffer then filtered through filter paper. The absorbance was recorded by using UV- spectrophotometer at 259 nm.

Viscosity Determination

The viscosity of the prepared hydrogel formulations was measured at room temperature by Brookfield viscometer (DV-II +) attached with spindle 64.The spindle was rotated

at varying rpm and readings were recorded to study the effect of shearing stress on viscosity.

Spreadability

Spread ability of formulations was determined by an apparatus suggested by Multimer, which was fabricated itself in laboratory and used for slide fixed on wooded block and upper slide with one end tide to glass slide and otherend tied with other end tied to weight pan. An excess of gel (2 gm) was placed in between two glass slides and then 200 gm weight was placed on slides for 5 min to compress the sample to a uniform thickness. Weight (80 gm) was added to pan. The time (seconds) required toseparate the two slides, was taken as a measure of Spreadability.
It was calculated using formula:
S = m. l / t
Where, S = Spreadability
m = weight tied to upper slide
l= length of glass slide
t = time taken

Shorter time interval, to cover distance of 6.5 cm, indicates better Spreadability.

Extrudability

The gel formulations were filled in standard caped collapsible tube and sealed. The tube was weighed recorded. The tube was placed between two glass slides and was clamped.After that 500 g weight was placed over the glass slide and then cap was opened. The amount of gel extruded were collected and weighed. The % of gel extruded was calculated; and grades were allotted (+ + + + excellent, + + + Good, + + fair, + Poor).

***In vitro* diffusion study**

Synthetic membrane was used as diffusion membrane. Membrane was soaked in phosphate buffer (pH 7.4) for 10 minutes before subjecting to diffusion study. The membrane was positioned between the two cell halves of a glass chamber. The two compartments were held together with a clamp. The receiver/ receptor compartment contained 40 ml of phosphate buffer (pH 7.4) and in the upper donor compartment 1 gm of formulation was spread evenly on the membrane. The receptor phase (phosphate buffer pH 7.4) was continuously stirred with help of magnetic stirrer and was maintained at temperature of 37 ± 1^0C during the experiments. One ml of the sample was withdrawn from the receiver compartment at time intervals 1/2, 1, 2, 3, 4, 5, 6, 7, 8 hrs and the same amount of fresh buffer solution was added to maintain the sink condition in receiver compartment. During the studies, care was taken to ensure that no air bubbles were trapped underneath the diffusion membrane.The samples were diluted up to 10 ml with phosphate buffer (pH 7.4) and were analysed spectrophotometrically at a wavelength of 259.0 nm. Percentage of fluconazole in each sample was determined by referring a previously prepared standard curve. This experiment was carried out for a period of 8 hours and in triplicate.

Table 2: cumulative amount of Fluconazole diffused (in %) from all the formulations through synthetic membrane using Franz diffusion cell.

Sr.no.	Time (hrs)	Cumulative amount of Fluconazole released (in %)			
		F1	F2	F3	F4
1	0.5	4.80 ±1.91	12.14 ± 3.12	6.12 ±2.01	0.88 ±0.48
2	1	9.10 ±2.22	15.92 ± 3.69	11.99 ± 2.96	3.94 ± 1.25
3	2	13.57 ±2.65	22.71 ± 4.88	18.16 ± 0.70	9.90 ± 0.56
4	3	19.90 ±4.59	32.28 ± 3.17	25.44 ± 1.90	15.91 ± 2.75
5	4	26.28 ±5.31	40.35 ± 3.09	33.05 ± 2.58	24.77 ±1.99
6	5	33.9 ±4.01	50.13 ± 3.78	41.73 ± 1.70	33.50 ± 1.91
7	6	41.76± 5.21	61.12 ± 5.46	51.79 ± 1.90	44.24 ± 0.87
9	7	50.80± 4.57	72.41 ± 4.05	62.05 ± 1.46	54.07 ± 0.70
10	8	60.43± 3.36	83.95 ± 4.18	75.31± 2.40	64.99 ± 0.99

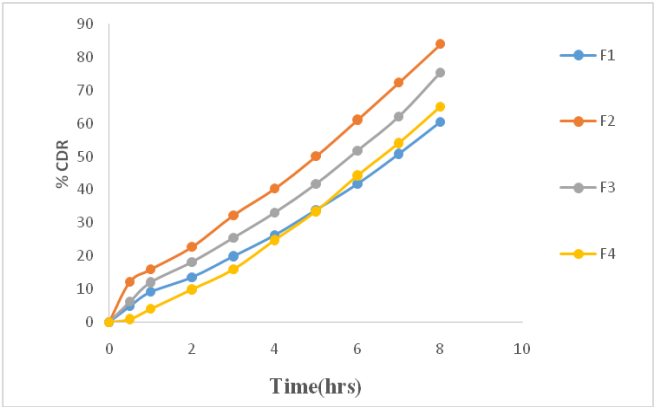

Figure 2: Cumulative amount of Fluconazole diffused (in %) from the formulations through synthetic membrane using Franz diffusion cell

Anti-fungal studies[5]

Weighed 16.25 gm of sabouraud dextrose agar was transferred in a 500 ml of conical flask and 250 ml of purified water and some amount of heat is applied to

dissolve it completely. Sterilized for 15 min at 121°C at 15 lb pressure in autoclave for about 20 min. Then cooled it at room temperature and the fungal strain(Candida albicans) was dispersed in the medium and then the medium was poured it in to the three Petri dish and allowed it cool it for some time at room temperature until it forms solidifies at room temperature and then the three cups are bored in each petridish with the help of sterile steel bore of 6 mm and gel formulations are placed in the bores and incubated the petri plates for 72 h at 37°C in incubators.

Stability study

Stability study of optimized formulation was carried out to point out any visual physical or chemical changes made in the formulation after storing it at elevated temperature and humidity conditions. Chemical and physical stability of optimized fluconazole formulation was assessed at room temperature and 40±2 ^{0}C/75±5% RH as per ICH Guidelines. Selected formulations (25 gm) were filled in container and stored for 3 months. Samples were analysed at 0, 30, 60, & 90 days for appearance, drug content, spreadability, pH and viscosity. The findings were recorded.

Table 3: Evaluation of Prepared formulations

Sr. no	Formulation	Viscosity at 5 rpm (Cp)	Extrudability	pH	Drug content (± S.D)	Zone of Inhibition (mm)
1	F1	83503	+	6.09 ± 0.012	98.81 ± 0.95	12
2	F2	64180	+ + +	6.05 ± 0.025	99.1 ± 0.65	17
3	F3	73784	+ +	6.02 ± 0.02	100.38 ± 1.69	14
4	F4	76130	+	6.17 ± 0.01	99.71 ± 1.61	12

RESULTS AND DISCUSSION

FT-IR study shows that Fluconazole is compatible with polymers as shown in figure 1. The prepared topical gel formulations have smooth homogeneous textureand translucentappearance. The pH value of all developed formulation was in range of 6.02-6.17 which lies in the normal pH range of the skin. The drug content of the formulated topical gel was estimated spectrophotometrically at λmax 259. The value of Spreadability indicates that the gel is easily spreadable by small amount ofshear. The extrusion of the gel from tube is important during its application. Gels with high consistency may not extrude from tube whereas, low viscous gel may flow quickly and hence suitable consistency is required in order to extrude the gel from the tube. Extrudability of optimized formulation was found to be good.

The vitro drug release profiles of fluconazole gel through synthetic membrane were studied. This data was compared for % drug release after 8 hours from various formulations. It was found that formulations preparedwith guar gum and Carbopol 934 in combination showed consistent and maximum drug release compared to the formulation prepared by single polymer Carbopol 934. F2 shows maximum drug release as compared to other formulations.Formulations are showing good zone of inhibition in antifungal activity is only due to fluconazole.

Topical gel formulations didn't indicate any manifestation of skin irritation such as redness of skin or inflammation at site of application. Thus, it may be concluded that all of the selected formulation are safe for topical application.Stability study shows that the prepared formulation is stable under the conditions of accelerated stability.

CONCLUSION:

Topical gel of Fluconazole was successfully prepared using two gelling agents i.e.carbopol 934 and guar gum. The IR studies suggest that polymer selected i.e. Carbopol 934, guar gumgumwas found to be compatible with fluconazole. The varying concentrations of two polymers were found to affect the gel parameters like drug release, spreadability and its viscosity.

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