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FORMULATION AND EVALUATION OF POSACONAZOLE TOPICAL GEL FOR THE TREATMENT OF FUNGAL INFECTIONS

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ABSTRACT:

Posoconazole is a potent antifungal medication used to treat various fungal infections. The development of a posoconazole gel formulation presents a promising approach to enhance drug delivery and efficacy. Gels are semi-solid emulsion systems that offers improved drug solubility and skin permeation.

The posoconazole gel formulation aims to provide sustained drug release, better skin penetration, and increased patient compliance compared to conventional dosage forms. The gel consists of an oil phase, water phase, emulsifying agents, gelling agents, and posoconazole as the active pharmaceutical ingredient. The gel is prepared using suitable techniques to ensure uniform drug distribution and stability.

Studies have shown that the posoconazole gel exhibits enhanced antifungal activity, reduced side effects, and improved patient outcomes. The gel formulation also offers advantages such as ease of application, non-sticky residue, and pleasant aesthetics, making it a favorable choice for topical antifungal therapy.

Keywords: Posaconazole, Carbopol 934, Sodium Alginate, HPMC E5, HPMC K100

INTRODUCTION:

Although there are various ailments available in the market for treatment of superficial fungal infections, still the fungal infections have been an unaddressed issue pertaining in present times. More than 50000 fungal species have been in to existence which is pathogenic to humans. (1) With the evolution in the fungal species genera there is evolution in the resistance of the fungal species too. The current antifungal therapy in the market includesanti-fungal drugs likeketoconazole, fluconazole, clotrimazole, posoconazole etc.(2)

Posaconazole formulations are also indicated in the prophylaxis of patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high-risk of developing invasive fungal infections and hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive

therapy for graft versus host disease and who are at high-risk of developing invasive fungal infections.(3) Posaconazole inhibits the enzyme lanosterol 14α-demethylase and consequently inhibits the biosynthesis of ergosterol, which is an essential component of fungal cell membrane. This results in an accumulation of methylated sterol precursors and depletion of ergosterol within the cell membrane, thereby weakening the structure and function of the fungal cell membrane, which is considered to be responsible for the antifungal activity of posaconazole.(4)

The main objective of the present study is to formulate and evaluate the topical antifungal gel containing posaconazole.

MATERIALS AND METHODS

MATERIALS:

Carbopol 934,sodium alginate, HPMC K100,HPMC E5, methyl paraben, propyl paraben and methanol were obtained from SD Fine-Chem Ltd, Mumbai, distilled water Laboratory made, Triethanolamine from Loba Chemie Pvt. Ltd, Mumbai. (5)

Preparation of gels

Various gel formulations were prepared using Carbopol 934, HPMC, and sodium alginate as gelling agents. Required quantity of gelling agent was weighed and dispersed in a small quantity of distilled water to form a homogeneous dispersion. In case of polymer like Carbopol the dispersion should be left for 24 h because of its swelling property. pH of the Carbopol gels was brought to skin pH (5.5 -7.0) by triethanolamine. Other excipients like methyl paraben and propyl paraben were also added with continuous stirring. The final weight was adjusted to 50g with distilled water. The gels were stored in wide mouthed bottles.(6)

Table 1: Gel formulations of posaconazole were prepared using carbopol 934 (F1), sodium alginate (F2) and HPMC (F3&F4)

CONTENTS	FORMULATION CODE			
	F1	F2	F3	F4
Posoconazole	0.5	0.5	0.2	0.2
Carbopol 934	1	-	-	-
Sodium Alginate	-	4	-	-
HPMC E5	-	-	3	-
HPMC K100	-	-	-	1
Triethanolamine	5	-	-	-
Methyl paraben	0.02	0.02	0.01	0.01
Propyl paraben	0.03	0.03	0.02	0.02
Distilled Water	q.s to 50	q.s to 50	q.s to 20	q.s to 20

Evaluation of gels

pH Measurement:

The pH of various gel formulations are determined by using digital pH meter.1 g of gel was dissolved in 100 ml. freshly prepared distilled water and stored for two hours. The measurement of pH of each formulation is done in triplicate and average values werecalculated.(7)

Viscosity Measurement:

Brookfield digital viscometer can be used to measure the viscosity of prepared gel formulations. The gels are rotated at 0.3, 0.6 and 1.5 rotations per minute. At each speed, the corresponding dial reading is noted (8). The viscosity of gel is obtained by multiplication of dial reading with factor given in the brookfield viscometer catalogues.

Spreadability:

Spread ability refers to the extent of area to which gel readily spreads on application. It is determined by wooden block and glass slide apparatus. The time in sec. taken by two slides to slip off from gel which is placed in between the slides under the direction of certain load is expressed as spreadability. Lesser the time taken for the separation of two slides, better the spread ability. (9) Spread ability is calculated by using the formula:

$S = M L / T$

Where,

S = Spread ability

M = Weight tide to the upper slide

L = Length of a glass slide

T = Time taken to separate the slide completely from each other. .

Grittiness- All the gel formulations are checked microscopically for the presence of any particulate matter.(10)

Drug content: 1 g gel is dissolved in 100 ml of suitable solvent. Absorbance is measured after suitable dilution at λmax nm using UV spectrophotometer. (11)

***In-vitro* drug diffusion study**: *In-vitro* drug release studies were carried out by using a Franz diffusion cell. 0.5 g of gel is taken in cellophane membrane. Diffusion studies are conducted at 37 °c± 10 °c employing 250 ml. phosphate buffer, pH 7.4 as the dissolution medium. sample were collected and replaced with new buffer solution. Collected samples were analyzed by using suitable analytical method.(12)

Homogeneity: Set the gel in container and then it were tested for homogeneity by visual inspection. They were tested for their appearance and presence of any aggregates.(13)

4. RESULTS & DISCUSSION:

Characterization of formulated gels

Physical appearance: The prepared formulation F1, F3, F4 were smooth, white in color and homogenous in appearance; F2 was brownish in color and homogenous in appearance.

pH measurement: The pH value of formulations are given in Table 2, which were in acceptable range to avoid skin irritation after application to the skin.

Drug content: The drug content for all the formulations were in acceptable range. The drug content of prepared formulations isgiven in Table 3

Viscosity: Viscosity is an important physical parameter which will reflect the consistency in case of topical preparations and it also affects the rate of posaconazole release. All formulations have adequate consistency. The viscosity values for F1- F4 were given in Table no. 4

Spreadability: The values of spreadability was given in Table 5 which indicate that the posaconazole formulations is easily spreadable by small amount of shear.

Table 2: pH of gel formulations

Formulation	pH
F1	6.2
F2	5.4
F3	6.6
F4	6.7

Table 3: Drug content of gel formulations

Formulation	Drug content%
F1	100.3
F2	99.95
F3	98.6
F4	97.6

Table 4: Viscosity of gel formulations

Formulation	Viscosity (cps)
F1	8467
F2	4252
F3	4459
F4	4530

Table 5: Spreadability of gel formulations

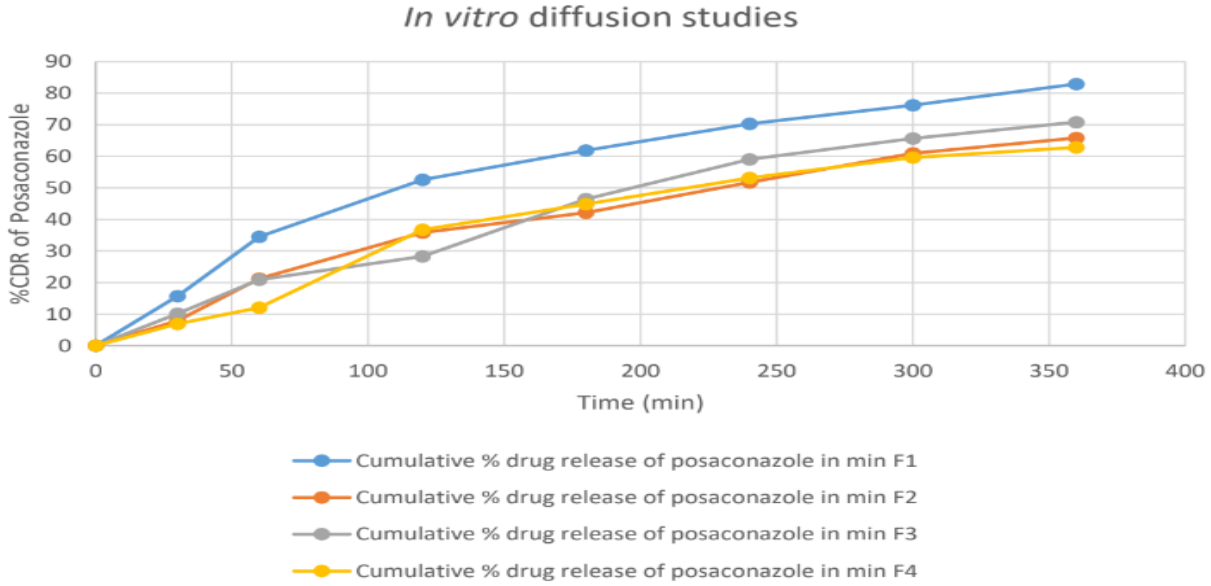
Formulation	Spreadability
F1	2.1
F2	1.9
F3	1.7
F4	1.5

***In-vitro* diffusion study:**

In vitro drug release studies were performed for formulations F1-F4. Franz diffusion cell (100ml cell volume) was used for the drug release studies. Posaconazole loaded F1, F2, F3, F4 (250 mg) was applied onto the surface of the dialysis membrane separately. The dialysis membrane is placed between the donor and the receptor chamber of diffusion cell. The receptor chamber was filled with freshly prepared 7.4 pH phosphate buffer solution to solubilize the drug. The receptor chamber was stirred by a magnetic stirrer and temperature is maintained at 37±1°cand at 50 RPM speed of magnetic bead. The samples (2 ml) were collected at a suitable time interval i.e.,30 min 1, 2, 3, 4, 5, 6 hours. The withdrawn volume was replaced with equal volume of fresh buffer solution. The drug release was determined by UV visible spectrophotometer at 252 nm.

Table 7: Cumulative % drug release of posoconazole

Time	Cumulative% drug release of posoconazole in min			
	F1	F2	F3	F4
30	15.67	7.87	10.18	6.91
60	34.51	21.28	20.95	12.05
120	52.51	35.87	28.26	36.74
180	61.64	42.15	46.42	44.83
240	70.28	51.73	59.03	53.18
300	76.17	60.95	65.70	59.62
360	82.93	65.82	70.85	62.83



CONCLUSION:

Posaconazole was developedas a as gel for topical drug delivery.Various formulations (F1, F2, F3 and F4) were developed by using a suitable polymer (carbopol 934, sodium alginate, HPMC E5, HPMC K100). Developed formulations of posaconazole were evaluated for the physicochemical parameters such as percentage yield, drug content, pH, viscosity, spreadability, and *in vitro* drug diffusion. The gels were translucent and rheological studies indicated that gels were non newtonian and pseudo plastic in behavior. All the four formulations show acceptable pH and optimum consistency. All the formulations are easily extrudable. The percentage drug content for all the formulations were found to be in the acceptable range (97.6-105.3). *In vitro*permeation studies were carried out for all the four formulations with different polymers. The formulation with the Carbopol (F1) showed the maximum drug release i.e., 82.93 % in 360 minutes. Results indicated that Carbopol gel show higher release of the drug compared to the other gelling agents. Hence, the prepared formulation could be used effectively for the treatment of topical fungal infections.

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