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Original Article

FORMULATION AND EVALUATION OF TOPICAL ANTIFUNGAL GEL CONTAINING ITRACONAZOLE

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ABSTRACT

Objective: The present research has been undertaken with the aim to develop a topical gel formulation of Itraconazole. Itraconazole is an imidazole derivative and used for the treatment of local and systemic fungal infection. The oral use of Itraconazole is not much recommended as it has many side effects. Commercially Itraconazole topical gel preparation are not available in the market, thus this formulation is made for better patient compliance and to reduce the dose of the drug and to avoid the side effects like liver damage and kidney damage.

Methods: The gel was formulated by changing the polymer ratio. Various formulation (F1, F2, F3, F4, F5) were developed by using a suitable polymer (carbopol 934p and HPMC). The formulation was evaluated for % yield, spreadability, extrudability, wash ability and viscosity *in vitro* drug release study, skin irritation study, stability testing.

Results: Viscosity studies of various formulations revealed that formulation F3 was better to compare to others. From among all the developed formulation, F3 shows better drug diffusion, did good Rheological properties. pH of the F3 formulation is sufficient enough to treat the skin infections. Results indicated that the concentration of carbopol-934 and HPMC K4M significantly affects drug release and rheological properties of the gels.

Conclusion: It was concluded that formulation F3 was the best formulation among this formulation. Hence formulation F3 should be further developed for scale-up to industrial production.

Keywords: Itraconazole, Carbopol 934p, HPMC

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INTRODUCTION

Fungal infection of the skin is nowadays one of the common dermatological problems. The physicians have a wide choice for treatment from solid dosage to semisolid dosage form and to liquid dosage formulation. Among the topical formulation, clear transparent gels have widely accepted in both cosmetics and pharmaceuticals [1]. Topical treatment of dermatological disease as well as skin care, a wide variety of vehicle ranging from solids to semisolids and liquids preparations is available to clinicians and patients. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparation [2]. For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, cream, gel, ointments, liquids, aerosols and injectable, as drug carriers. Delivery of drugs to the skin is an effective and targeted therapy for local dermatological disorders. This route of drug delivery has gained popularity because it avoids first-pass effects, gastrointestinal irritation, and metabolic degradation associated with oral administration. Due to the first past effect, only 25-45% of the orally administered dose reaches the blood circulation. In order to bypass these disadvantages, the gel formulations have been proposed as a topical application. Gels are defined as "semisolid system in which a liquid phase is constrained within a polymeric matrix in which a high degree of physical and chemical cross-linking introduced". Itraconazole is a synthetic antifungal agent of the imidazole class; it works by slowing the growth of fungi that cause infection. It is used to treat fungal infection. Triazole drug targets the fungal-specific synthesis of membrane lipids. Itraconazole inserts preferentially into fungal membranes and disrupts their function. 5-fluorocytosine targets fungal-specific DNA replication [3]. Hydroxypropyl methylcellulose (HPMC), Carbapol 934p, has been used as hydrophilic polymers topically in gel drug delivery system [4].

MATERIALS AND METHODS [5, 6]

Material

Itraconazole, HPMC, carbopol934, trimethanolamine, glycerine, Methylparaben, propylparaben, water.

Method

Polymer (like Carbopol 934p or HPMC) and purified water were taken in a beaker and allowed to soak for 24 h. To this required amount of drug (2 gm) was dispersed in water and then Carbopol 934p or HPMC was then neutralized with sufficient quantity of Triethanolamine. Glycerine as a moistening agent, methylparaben and Propylparaben as preservatives were added slowly with continuous gently stirring until the homogenous gel was formed.

Gel formulations of Itraconazole were prepared using different concentrations of carbopol934, HPMC.

Table 1: Optimized formulae of Itraconazole gel

Formulation code	Ingredients								
	Drug	Carbopol	HPMC	Water	Alcohol	Methyl	Propyl	Glycerine	Triethanol
F1	2	1	-	60	4	0.1	0.05	10	4
F2	2	1	-	60	4	0.1	0.05	10	4
F3	2	0.5	0.75	60	4	0.1	0.05	10	4
F4	2	0.5	0.5	60	4	0.1	0.05	10	4
F5	2	0.75	0.5	60	4	0.1	0.05	10	4

Evaluation of itraconazolegel [7-24]

Percentage Yield

The empty container was Weighed in which the gel formulation was stored then again the container was weighed with gel formulation. Then subtracted the empty container weighed with the container with gel formulation then it gives the practical yield. Then the percentage yield was calculated by the formula.

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Drug content

Weighed 10 gm of each gel formulation were transferred in 250 ml of the volumetric flask containing 20 ml of alcohol and stirred for 30 min. The volume was made up to 100 ml and filtered. 1 ml of the above solution was further diluted to 10 ml with alcohol and again 1 ml of the above solution was further diluted to 10 ml with alcohol. The absorbance of the solution was measured spectrophotometrically at 260 nm. Drug content was calculated by the following formula

$$\text{Drug content} = \frac{\text{Absorbance}}{\text{Slope}} \times \text{Dilution factor} \times \frac{1}{1000}$$

Determination of Ph

Weighed 50 gm of each gel formulation were transferred in 10 ml of the beaker and measured it by using the digital pH meter. pH of the topical gel formulation should be between 3–9 to treat the skin infections.

Spreadability

The spreadability of the gel formulation was determined, by measuring the diameter of 1 gm gel between horizontal plates (20×20 cm2) after 1 minute. The standardized weight tied on the upper plate was 125 gm.

Extrudability

The gel formulations were filled into a collapsible metal tube or aluminium collapsible tube. The tube was pressed to extrude the material and the extrudability of the formulation was checked.

Viscosity estimation

The viscosity of gel was determined by using a Brookfield viscometer DVII model with a T-Bar spindle in combination with a helipath stand.

a) **Selection of spindle**: Spindle T 95 was used for the measurement of viscosity of all the gels.

b) **Sample container size**: The viscosity was measured using 50 gm of gel filled in a 100 ml beaker.

c) **Spindle immersion**: The T-bar spindle (T95) was lowered perpendicular in the centre taking care that spindle does not touch the bottom of the jar.

d**) Measurement of viscosity**: The T-bar spindle (T95) was used for determining the viscosity of the gels. The factors like temperature, pressure and sample size etc. Which affect the viscosity was maintained during the process. The helipath T-bar spindle was moved up and down giving viscosities at a number of points along the path. The torque reading was always greater than 10%. The average of three readings taken in one minute was noted as the viscosity of gels.

***In vitro* diffusion study**

The abdominal skin of Albino mice, weighing 20–25 gm of 8–10 w old was shaved using hand razor and clean the skin with hot water cotton swab. 5 gm of gel was applied uniformly to the skin. The skin was mounted between the compartments of the Frantz diffusion cell with stratum corneum facing the donor compartment. Reservoir compartment was filled with 100 ml phosphate buffer of pH 6.8. The study was carried out at 37±1 °C and the speed was adjusted until the vortex touches the skin and it carried out for 4½ h. 5 ml of the sample was withdrawn from the reservoir compartment at 30 min interval and absorbance was measured spectrophotometrically at 260 nm. Each time the reservoir compartment was replenished with the 5 ml volume of phosphate buffer pH 6.8 solution to maintain a constant volume.

RESULTS AND DISCUSSION

Table 2: Percent yield of gel formulations

Formulation	Percent yield
F1	99.59%
F2	98.34%
F3	97.44%
F4	99.81%
F5	98.76%

Table 3: Drug content of gel formulations

Formulation code	Drug content
F1	94.41
F2	97.38
F3	98.24
F4	96.52
F5	95.07

Table 4: pH of gel formulations

Formulation	Ph
F1	6.98
F2	7.01
F3	6.98
F4	6.5
F5	6.79

Table 5: Viscosity of gel formulations

Formulation	Viscosity(cp)
F1	8476
F2	4259
F3	4450
F4	4544
F5	6.79

Table 6: Spreadability of gel formulations

Formulation	Spreadability	
	R1	R2
F1	1.3	1.9
F2	2.1	2.9
F3	19	2.8
F4	1.7	2.3
F5	1.5	2.1

Table 7: Extrudability of gel formulations

Formulation	Extrudability
F1	+
F2	+++
F3	+++
F4	++
F5	++

Excellent (+++), Good (++), Average (+), Poor (-)

Table 8: *In vitro* diffusion chart

Time	% CDR				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
30	12.95	16.87	14.88	14.03	13.67
60	39.51	44.39	41.39	40.76	40.05
90	47	48.49	47.95	47.02	46.91
120	56.59	56.01	57.18	56.24	55.74
150	62.84	61.28	63.59	62.31	61.89
180	71.84	72.69	73.26	72.13	71.84
210	80.17	79.37	82.15	81.68	80.86
240	87.27	86.16	89.07	88.19	87.98
270	95.98	94.09	97.03	96.83	96.03

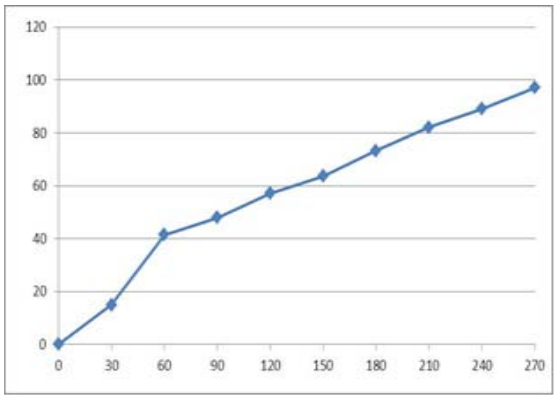

Fig. *In vitro* diffusion for F3 formulation

CONCLUSION

Various formulation (F1, F2, F3, F4, F5) were developed by using a suitable polymer (carbopol 934p and HPMC). Developed formulations of Itraconazole were evaluated for the physiochemical parameters such as percentage yield, drug content, pH, viscosity, spreadability, extrudability, *in vitro* drug diffusion. Viscosity studies of various formulations revealed that formulation F3 was better to compare to others. From among all the developed formulation, F3 shows better drug diffusion, did good Rheological properties. pH of the F3 formulation is sufficient enough to treat the skin infections. Results indicated that the concentration of carbopol-934 and HPMC K4M significantly affects drug release and rheological properties of the gels. The viscosity of carbopol-934 gels was very high as compared to HPMC K4M gels but both gels showed a decrease in drug release with an increase in polymer concentration. Thus, gels can be successfully prepared using carbopol-934 and Hydroxypropyl methylcellulose as gelling agents in the ratio 1:3(carbopol-934 and Hydroxypropyl methylcellulose) suitable for topical application Hence formulation F3 should be further developed for scale-up to industrial production.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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