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Formulation & evaluation of fluconazole gel

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ABSTRACT

Fluconazole is a synthetic triazole with antifungal activity. Fluconazole preferentially inhibits fungal cytochrome P-450 sterol C-14 alpha-demethylation, resulting in the accumulation of fungal 14 alpha-methyl sterols, the loss of normal fungal sterols, and fungi static activity. Fluconazole is also used to prevent fungal infection in people who have a weak immune system caused by cancer treatment, bone marrow transplant, or diseases such as AIDS. Fluconazole is also used to treat a certain type of meningitis in people with HIV or AIDS. The gel was formulated by changing the polymer ratio. The present study was designed to formulate and evaluate different formulae of topical gel containing fluconazole for treatment of fungal infection of skin. The gel was formulated by using different polymers with different concentration as Carbopol 940, Hydroxypropyl methylcellulose E4M, Methyl cellulose, Pectin and Pluronic P407. Ten different formulae were prepared and characterized physically in term of colour, syneresis, spread ability, pH, drug content and rheological properties. In-vitro drug release in phosphate buffer pH 5.5 and permeation study through cellulose membrane, using a modified Franz diffusion cell, were performed. The results of in vitro drug release and its permeation studies showed that the highest values were from F3(91.3% of drug released after 2 hr). Also, F3 shows the highest antifungal activity.

Keywords: Fluconazole, Antifungal activity, Pectin, propylene glycol.

INTRODUCTION

Topical preparations are formulae which are applied directly to an external body surface by spreading, rubbing, spraying or instillation. The topical route of administration has been utilized either to produce local effect for treating skin disorder or to produce systemic drug effects. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. Gels often provide a faster release of drug substance, independent of the water solubility of the drug, as compared to creams and ointments. They are highly biocompatible with a lower risk of inflammation or adverse reactions, easily applied and do not need to be removed. Gels are semisolid dosage form. In that dispersion of small or large molecules in an aqueous liquid vehicle. They produced jelly like consistency by the addition of a gelling agent. Medicated gels prepared for administration by various routes for eye, nose, vaginal and rectum. Fluconazole 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.

MATERIALS

HMPC, Carbopol 940, Methly Pectin, Pluronic F127, Methyl paraben, Propyl paraben, Glycerine, Propylene glycol.

EQUIPMENTS

Electron analytical balance**,** UV-visible spectrophotometer**,** Fourier Transform Infrared Spectroscope**,** pH Tutor**,**

Magnetic stirrer**,** Franz diffusion cell**,** Brookfield viscometer.

PREPARATION OF FLUCONAZOLE TOPICAL GELS

The composition of fluconazole topical gel formulae is shown in table 4. Fluconazole (1% w/w) was dissolved in a hot mixture containing propylene glycol (20% w/w) and glycerine (10% w/w) as moistening agent. Polyacrylic acid polymer (carbopol 940), cellulose polymers (HPMC, MC), polysaccharide polymer (Pectin) gel were prepared by dispersing the calculated amount of polymer in calculated amount of warm water with constant stirring using magnetic stirrer at a moderate speed. Then add the previous mixture containing the drug. The pH of carbopol gel was adjusted using TEA. While polymer undergoing transition (Pluronic) was dispersed slowly in cold water 4ºC with constant stirring according to cold technique. Finally, methyl and propyl paraben as preservatives were added slowly with continuous stirring until gel formation. The prepared gels were packed in wide mouth glass jar covered with screw capped plastic lid after covering the mouth with an aluminum foil and were kept in dark and cool place.

Table 1: Composition of Fluconazole Topical Gel (% w/w)

Ingredients	F1	F2	F3	F4	F5	F6 (Marketed Product)
Fluconazole	1	1	1	1	1	1
Carbopol	940	0.5	1	-	-	-
HPMC	-	-	1.5	2	-	-
Methyl Cellulose	-	-	-	-	2	4
Pectin	-	-	-	-	-	-
Pluronic F127	-	-	-	-	-	-
Glycerin	10	10	10	10	10	10
Propylene glycol	20	20	20	20	20	20
Methyl Paraben	0.03	0.03	0.03	0.03	0.03	0.03
Propyl Paraben	0.01	0.01	0.01	0.01	0.01	0.01
Purified water upto	100	100	100	100	100	100

EVALUATION OF PREPARED FLUCONAZOLE Gels

1. Visual examination

All developed gel formulae were inspected for their homogeneity, colour, syneresis and presence of lumps by visual inspection after the gels have been set in the container.

2. Spread ability test

A sample of 0.5 g of each formula was pressed between two slides (divided into squares of 5 mm sides) and left for about 5 minutes where no more spreading was expected Diameters of spreaded circles were measured in cm and were taken as comparative values for spread ability.

3. pH determination

The results obtained are average of three determinations. Results are shown in table 4. The pH of the gels was determined using digital pH meter. Weighed gram of each gel formulation were transferred in 10 ml of beaker and measured it by using the digital pH meter. The readings were taken for average of 3 times.

4. Drug Content determination

A specific quantity of developed gel was taken and dissolved in 100ml of phosphate buffer of pH 5.5. The volumetric flask containing gel solution was shaken for 2 hour on mechanical shaker in order to get complete solubility of drug. This solution was filtered using Millipore filter (0.45µm). After suitable dilution drug absorbance was recorded by using UV-visible spectrophotometer (UV – 1700) at λ max 260 nm using phosphate buffer (pH 5.5) as blank.

5. Rheological Studies

The viscosity of the different gel formulae was determined at 25°C using rotational Brookfield viscometer of cone and plate structure with spindle CPE-41 and CP-5221. The apparent viscosity was determined at shear rate 40 sec-1. The flow index was determined by linear regression of the logarithmic.

6. In Vitro Release Studies

The study was carried out using (dissolution tester, model). One gram of fluconazole was placed in the watch glass covered with aluminium mesh. The watch glass was then immersed in the vessel containing 500 ml of the release medium, phosphate buffer pH 5.5 at 37ºC ± 0.5ºC with a paddle speed of 50 rpm. Aliquots (5ml) were withdrawn at specified time intervals every 10 minute over 2 hours and immediately replaced with fresh dissolution medium. The samples were assayed spectrophotometrically at λmax 260 nm and the concentration of the drug was determined from the previously constructed calibration curve. Experiments were carried out in triplicates, the results were averaged and blank experiments were carried using plain bases.

7. Drug Release Kinetic Study

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

a- Zero – order equation:
Q = kot
Where, Q is the amount of drug released at time t, and k t 0 is the zero – order release rate.

b- First – order equation:
In (100 – Q) = In 100 – k1
Where, Q is the percent of drug release at time t, and k t1

c- Higuchi's equation: is the first – order release rate constant.

$Q = k\,t$

Where, Q is the percent of drug release at time t, and k 1/2 is the diffusion rate constant

8. In-vitro Drug Diffusion Study

Cellulose membrane (0.45µm, obtained from sigma chemicals) was used for this study. A sample of 1g of the preparation was spreaded on a cellulose membrane previously soaked overnight in the release medium. The loaded membrane was firmly stretched over the edge of a glass tube of 2 cm diameter; the membrane was tied up with a rubber to prevent leakage. Tubes were then immersed in the dissolution vessel which contained 50 ml of the release medium, phosphate buffer pH 5.5, and maintained at 37ºC ± 0.5ºC25.

9. Antifungal study

The prepared formulae were tested in a triplicate manner using agar cup method against Candida albican strain. Cup of 10 mm in diameter were made aseptically in Sabouraud dextrose agar after being inoculated with tested fungal suspension strain by spreading on the agar surface. The cups were filled with each prepared formula by sterile syringe. Then the zone of inhibition of each cup was observed and calculated the radius of the zone of inhibition and compared to the control formula.

RESULTS AND DISCUSSION

1. Visual examination

Table 2: Visual Examination of Fluconazole Topical Gels

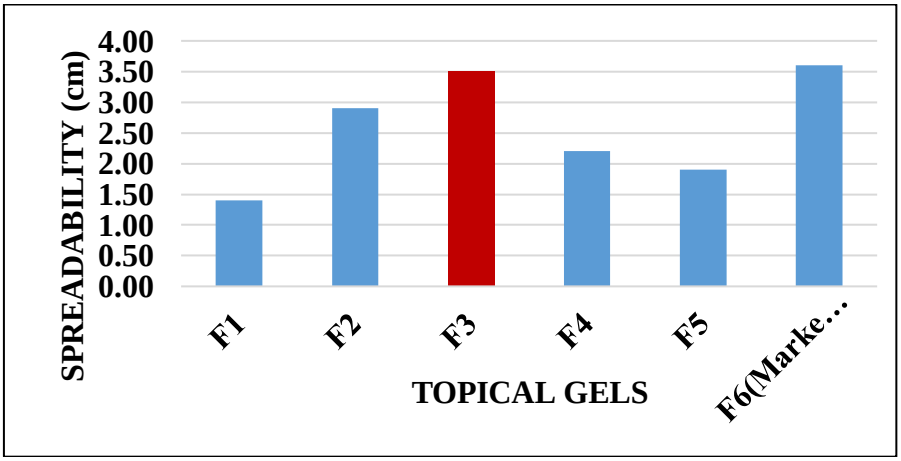
Topical Gels	Color	Synerisis
F 1	Shiny transparent	-ve
F 2	Shiny transparent	-ve
F 3	Transparent	-ve
F 4	Transparent	-ve
F5	Translucent yellowish	-ve
F6 (Marketed Product)	Translucent yellowish	-ve

The prepared gel formulae were inspected visually for their color and syneresis. The developed preparations were much clear and transparent

2. Spread ability

Table 3: Spread ability Test of Fluconazole Topical Gels

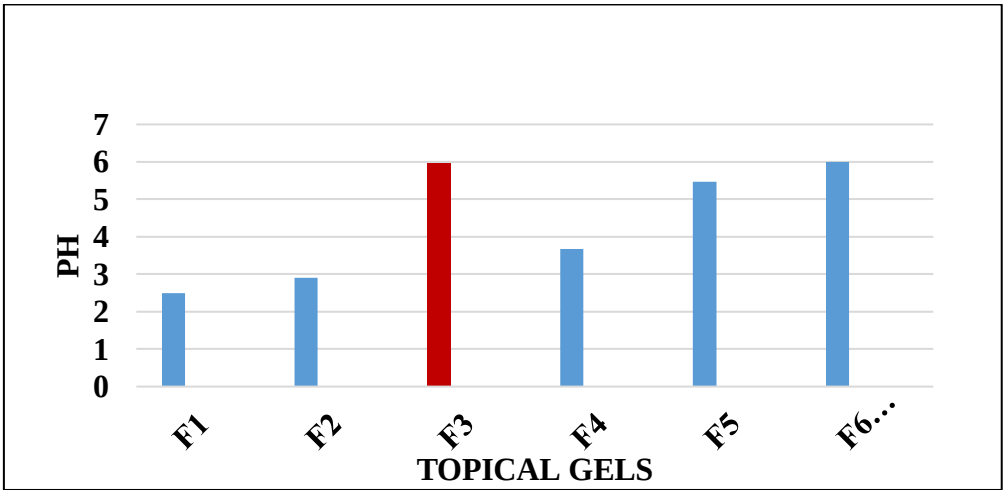
Topical Gels	Spredablity (cm)
F 1	1.4
F 2	2.9
F 3	3.5
F 4	2.2
F5	1.9
F6 (Marketed Product)	3.6



3. pH Determination

Table 4: PH Determination of Fluconazole Topical Gels

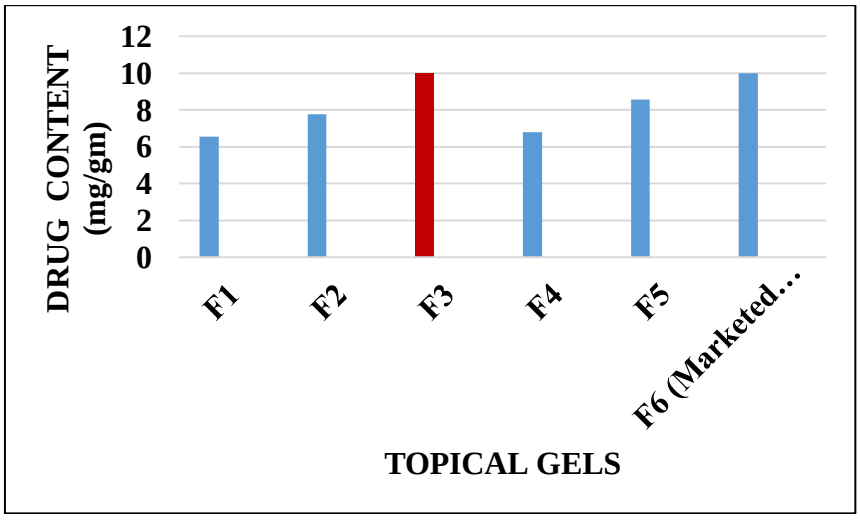
Topical Gels	pH
F 1	2.49
F 2	2.9
F 3	5.97
F 4	3.67
F5	5.47
F6(Marketed Product)	6



4. Drug Content determination

Table 5: Drug Content Determination of Fluconazole Topical Gels

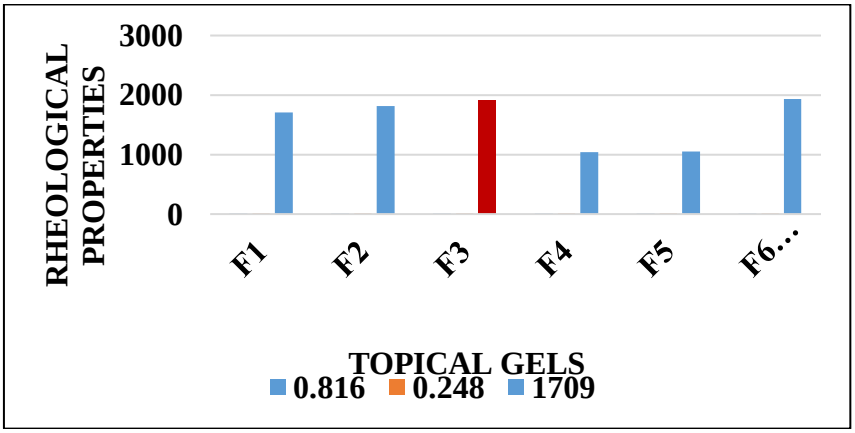
Topical Gels	Drug content (mg/gm gel)
F 1	6.55
F 2	7.77
F 3	9.99
F 4	6.78
F5	8.58
F6(Marketed Product)	9.98



5. Rheological properties

Table 6: Rheological properties of Fluconazole Topical Gels

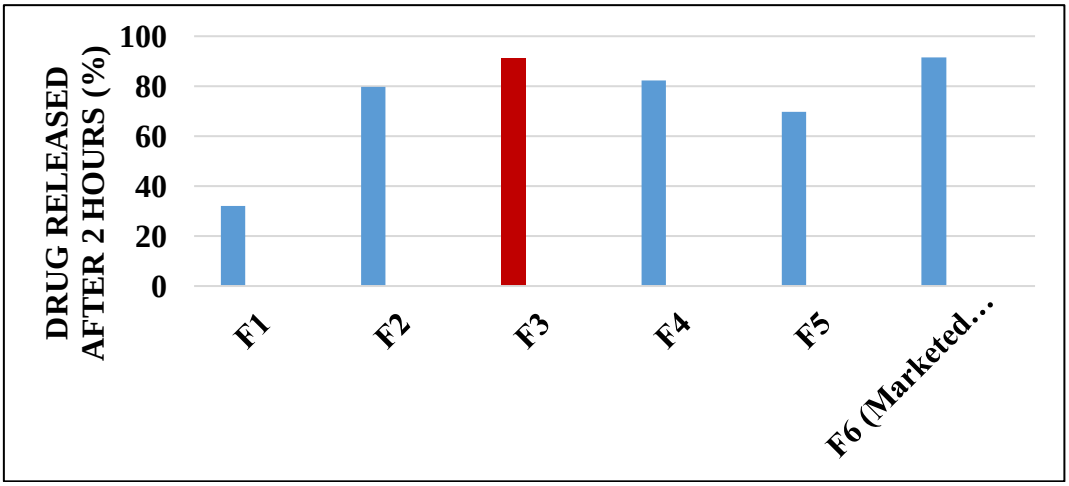
Formula no.	Coefficient determination	Flow Index (n)	Viscosity* (centipoise) (η)	Flow Behavior
F 1	0.816	0.248	1709	Shear thinning
F 2	0.659	0.210	1818	Shear thinning
F 3	0.997	0.260	1912	Shear thinning
F 4	0.532	0.110	1036	Shear thinning
F5	0.908	0.130	1049	Shear thinning
F6 (Marketed Product)	0.998	0.275	1938	Shear thinning



6. In-Vitro Release Studies

Table 7: In vitro release studies of Fluconazole Topical Gels

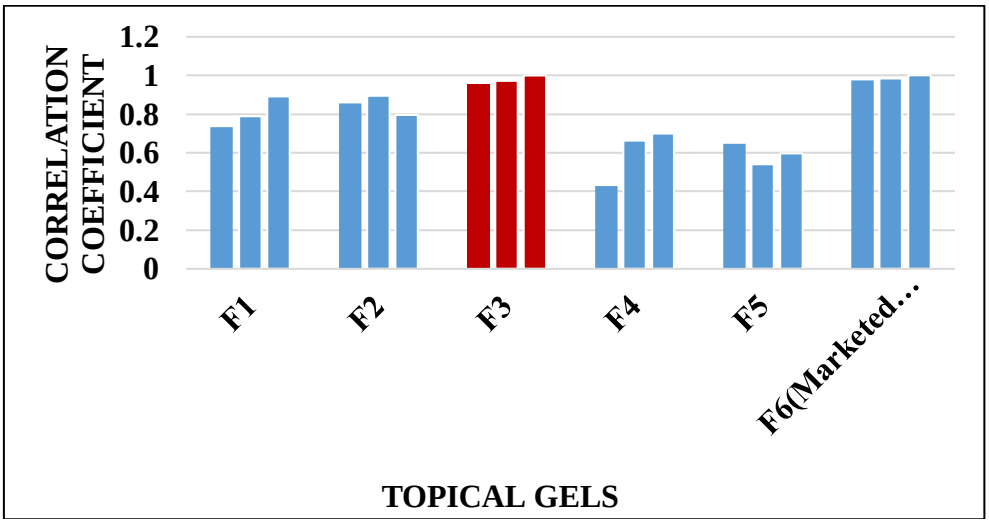
TOPICAL GEL	DRUG RELEASED AFTER 2 HOURS (%)
F1	32.1
F2	79.6
F3	91.3
F4	82.3
F5	69.8
F6 (Marketed product)	91.5



7. Drug Release Kinetic Study

Table 7: Kinetic study of in vitro release data of fluconazole from different formulae

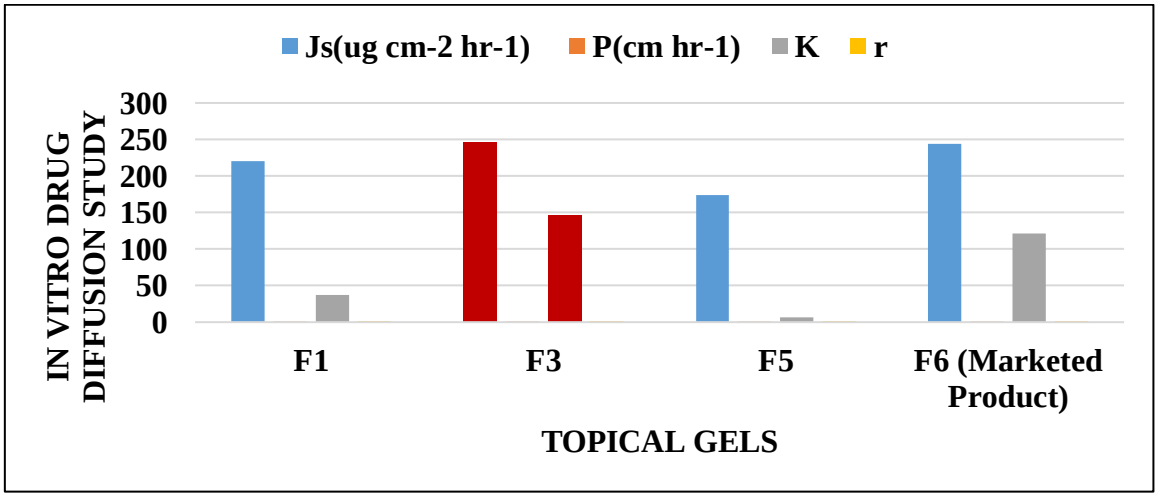
Formula №	Correlation Coefficient(R2)		
	Zero order	First order	Diffusion
F1	0.7339	0.7896	0.8929
F2	0.8549	0.8958	0.7960
F3	0.9527	0.9722	0.9998
F4	0.4268	0.6628	0.6994
F5	0.6451	0.5393	0.5975
F6(Marketed Product)	0.9738	0.9838	0.9999



8. In-vitro Drug Diffusion Study

Table 8: In vitro Drug Diffusion Study of the Selected Topical Gels

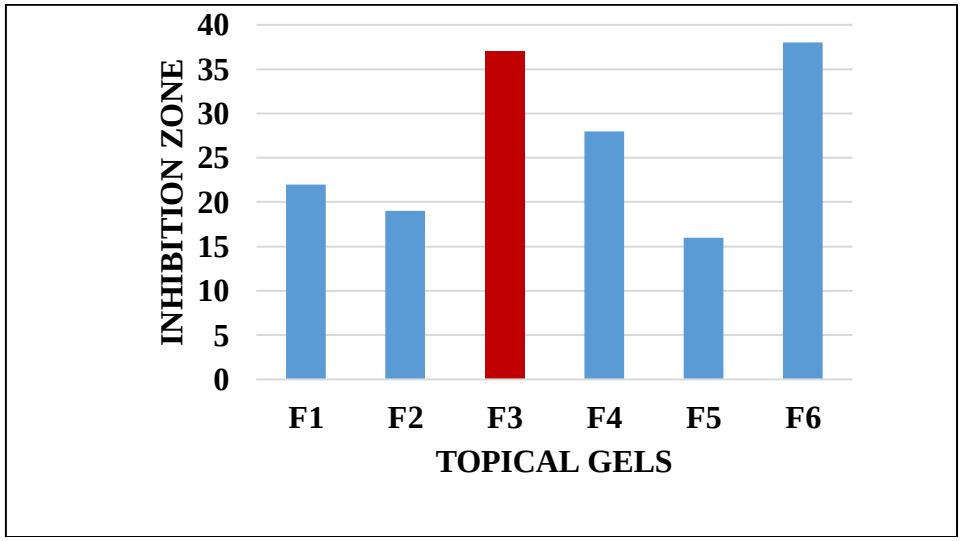
Topical gel	Js(ug cm^{-2} hr^{-1})	P(cm $hr^{-1)}$	K	r
F1	220.63	0.002	36.94	0.8475
F3	246.37	0.024	146.53	0.9999
F5	174.23	0.011	6.76	0.9897
F6 (Marketed Product)	243.83	0.024	121.66	0.9997



9. Antifungal study

Table 9: Inhibition zone of the prepared topical gel formulae

Formulation	Inhibition Zone
F1	22
F2	19
F3	37
F4	28
F5	16
F6 (Marketed Product)	37.5



CONCLUSION

In the present study, an attempt was made to formulate topical gel of fluconazole for efficient delivery of drug across the skin. Preformulation study for drug-excipients compatibility by FT-IR showed no interaction between drug and selected excipients. Various formulation (F1, F2, F3, F4, F5...) were developed by using suitable polymer (carbopol 934p) and penetration enhancer. Developed formulations of fluconazole were evaluated for the physiochemical parameters such as drug content, viscosity, spread ability, in vitro diffusion.Viscosity studies of various formulations revealed that formulation F3 was better compare to others. Skin irritation study indicated that no irritation has been produced by gel formulation F3. Anti-fungal studies also showed the good results of formulation F3. On the basis of the previous findings we can concluded that Fluconazole was successfully incorporated into the different topical gel preparations. From among all the developed formulation the formula F 3 shows good spread ability, drug release and antifungal effect. F3 is found to be near the marketed product F6. Therefore, it was concluded that our formulae could be very promising topical alternative for the treatment of skin fungal infections. However, further preclinical and clinical studies are required.

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