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FORMULATION DEVELOPMENT AND EVALUATION OF FLUCONAZOLE GEL IN VARIOUS POLYMER BASESFORMULATION DEVELOPMENT AND EVALUATION OF FLUCONAZOLE GEL IN VARIOUS POLYMER BASES

SANJAY, BIDKAR DEVENDRA JAIN*, AMOL PADSALG, KRISHNA PATEL AND VINOD MOKALE

1AISSMS College of Pharmacy, Kennedy road, Near RTO, Pune-411001.

E-mail: sgbpharmacon@gmail.com

ABSTRACT

Topical drug delivery systems of Fluconazole, antifungal drug in the form of gels were formulated using polymers like HPMC, Carbopol 934, Methylcellulose and Sodium alginate. The gels were evaluated for various physicochemical parameters like pH, viscosity, rheology, drug content, spreadibility and skin irritation test. In addition, in vitro drug release by diffusion using cellophane membrane and permeation through hairless rat skin using modified Kiesery Chien Diffusion cell was performed. The rheological behaviour and apparent viscosity values for different gel bases were measured before and after storage under freezing condition at 2-8 ^{0}C and were taken as measure for stability of gel network structure. Also accelerated stability testing at 45±2 ^{0}C and 75%±5% R.H for 3 months were performed. Among the four formulations, gel prepared using HPMC shows desired properties and exhibit better release pattern when compared with other formulations prepared with Carbopol, Sodium alginate and Methylcellulose.

Keywords : Fluconazole, Gel, permeation study, rheology

INTRODUCTION

For the topical treatment of dermatological diseases, a wide choice of vehicles ranging from solids to semisolids and liquid preparations are available to clinicians and patients. Within the semisolid preparations transparent gels are widely used in cosmetic pharmaceuticals [1, 2]. Out of various semisolid dosage forms, gels are becoming more popular due to ease of application and better percutaneous absorption. Typical three-dimensional structures, characteristics of the gels, come from the links among the polymer chains [3]. Gels can resist the physiological stress caused by the skin flexion, blinking and mucociliary movement, adopting the shape of the applied area and controlling drug release[4-7]. Effectiveness of the topical application mainly depends upon its rate and extent of drug release from the base.

Fungal infections are common in human beings, which are either topical or severe systemic infections. Invasive fungal infections are being identified with an ever-ncreasing frequency in prematured infants, immunocompromised hosts, and patient's receiving immunosuppressive agents and in those with acquired immuno deficiency syndrome (AIDS). The prevention of fungal infections has been improved by the antifungal agent such as Fluconazole[8].

Fluconazole, a recent triazole antifungal drug is used in the treatment of superficial and systemic fungal infection. The drug has slight solubility in water (8mg/ml), melting point of 138-142^{0}C and is widely available as tablets and IV infusion[9, 10]. Topical drug delivery system localizing the drug at skin will be much favorable for the treatment of skin infections and symptomatic relief. In the present work, topical drug delivery system like gels, formulated using HPMC, Carbopol 934, Methylcellulose and Sodium alginate are evaluated with the view to develop localized drug delivery system of Fluconazole.

MATERIALS AND METHODS

Materials

Fluconazole was a gift sample from IATROS pharmaceuticals pvt. Ltd, Pune. The polymers Hydroxy Propyl Methyl Cellulose (HPMC) 4000cps, Methylcellulose (MC) were purchased from Colorcon Asia, Goa and Carbopol 934, Sodium alginate from Loba Chemicals, Mumbai. All other chemicals used were of analytical grade.

Methods

Preparation of gels

The polymer and purified water I.P. were taken in a mortar and allowed to soak for 24hrs and to this required amount of drug and other additives were added. The trituration was continued to get homogenous dispersion of drug, Fluconazole 0.5%w/w.

Evaluation of gels

Drug content evaluation –

Drug content was determined by dissolving accurately weighed quantity of gels in methanol (AR grade). After suitable dilution absorbance was recorded by using UV spectrophotometer (Jasco V 530 UV/VIS Spectrophotometer) at 260nm. Drug content was determined using slope of standard curve, previously plotted.

pH

2.5gm of gel was accurately weighed and dispersed in 25ml of purified water. The pH of dispersions was measured using pHmeter (systronics digital-DI-707).

Viscosity and Rheological studies

Viscosities of gels were determined using Brookfield Viscometer. Gels were tested for their rheological characteristics at 250C using Brookfield Viscometer (DV-III programmable Rheometer). The measurement was made over the whole range of speed settings from 10rpm to 100rpm with 30seconds between 2 successive speeds and then in a descending order.

Spreadibility [11]

For the determination of spreadibility excess of sample was applied in between two glass slides and was compressed to uniform thickness by placing 1000gm weight for 5minutes. Weight (50gm) was added to the pan. The time required to separate the two slides, i.e. the time in which the upper glass slide moves over the lower plate was taken as measure of spreadibility (s).

$S = ml/t$

Where m = weight tide to upper slide

l = length moved on the glass slide

t = time taken.

Invitro **diffusion study**

Cellophane membrane[12] obtained from sigma chemicals was used for this study. In modified Kiescary Chien diffusion cell, 2gm of gel was kept in donor compartment. The entire surface of membrane was in contact with the receptor compartment containing 22ml of phosphate buffer pH 7.4. The receptor compartment was continuously stirred (100rpm) using a magnetic stirrer. The temperature maintained was 37 ± 1^0C. The study was carried out for 12hr with the interval of 1, 2, 3, 4, 5, 6, 9, 12hr. The surface area available for diffusion was calculated and was found to be 3.14cm^2. The sample was withdrawn at predetermined time interval and same volume was replaced with fresh phosphate buffer. The absorbance of withdrawn sample was measured after suitable dilution at 260nm to estimate Fluconazole. The experiment was carried out in triplicate and average values are reported.

Invitro **permeation studies**

Kiescary Chien diffusion cell mounted with hairless rat skin was used for drug permeation study. 2gm of gel was taken into the cell (donor compartment) and phosphate buffer pH 7.4 in receptor compartment which is agitated using magnetic stirrer (100rpm) and temperature maintained to 37 ± 1^0C was maintained. The sample was withdrawn at predetermined time intervals and same volume replaced with fresh buffer medium. Absorbance was measured after suitable dilution at 260nm to estimate Fluconazole.

Stability Studies

Formulated gel preparations were kept at different temperature condition like ambient temperature (R.T), 8 ± 1^0C (refrigerator temperature), 45 ± 2^0C at 75%±5% R.H. (condition of accelerated stability testing) for span of three months. The following parameters of the gel such as color, pH, viscosity and drug content were studied.

Skin irritation test

The skin irritation test was performed on white rabbit, by applying 1gm gel formulation on 9cm2 area, saturated drug solution (1ml) soaked in 9cm2 cotton wool. An aqueous solution of 1ml, containing 0.8% formalin soaked in 9cm^2 cotton wool (standard irritant) was placed in the back of the rabbit. The cotton wool was secured firmly in the place with adhesive plaster. The animal was observed for 7 days for any sign of edema and erythrema.

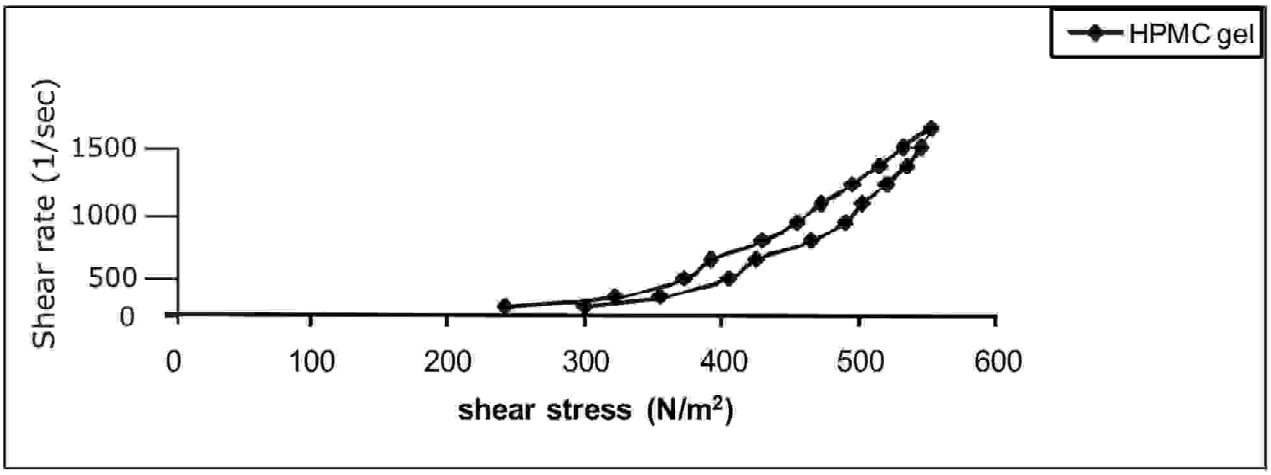
RESULTS AND DISCUSSION

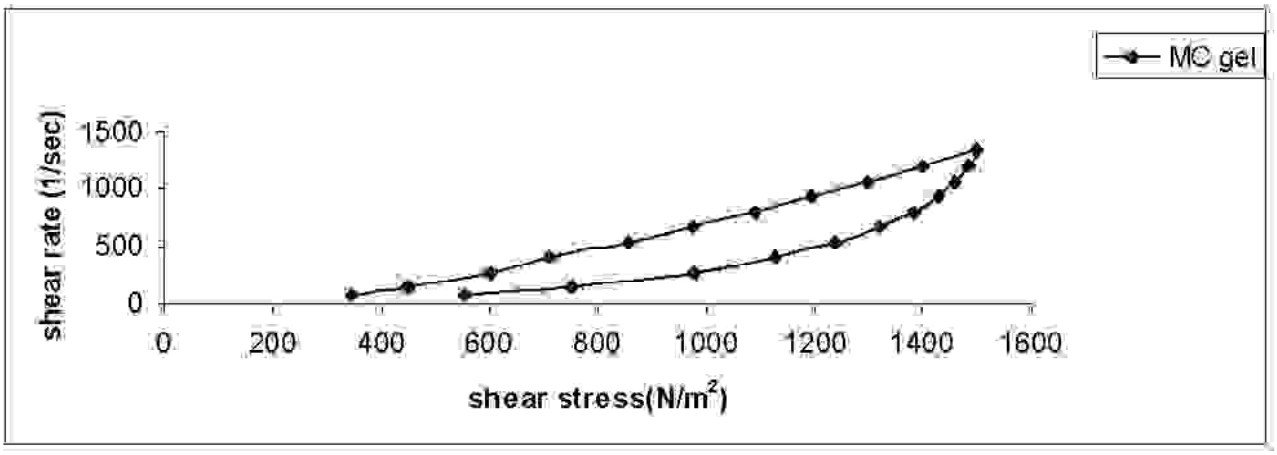
In the present study efforts were made to prepare gels of Fluconazole using polymers like HPMC (4000cps), MC,

Carbopol 934, Sodium alginate. Gels prepared with HPMC, MC and Carbopol were found to be translucent and homogenous while Sodium alginate gel was brownish and Homogenous. Drug content of the formulations was well within the range between 96-99% (table2) and pH 7.00-7.50 (table2). Spreadibility of all gel formulations was shown in table-2 and did not produce any skin irritation.

The viscosity of various formulated fluconazole gels was measured using a Brookfield viscometer shown in table 2. The rheological behaviour of all formulated gels systems were studied and shown in figure 1. In gel systems, consistency depends on the ratio of solid fraction, which produces the structure, to liquid fraction. Differences in concentration and kind of gelling agents result in changes in the occurring structure consistency16. Apparent viscosity and rheological behaviour of the formulation lead to the consistency. The shape of the rheogram indicates that HPMC and carbopol gel are easier to apply than other gels.

The release rate from cellophane membrane and through hairless rat skin was studied and found to be in the same order i.e. HPMC>Carbopol>MC>Sodium alginate as shown in figure 2 and figure 3. The amount of Fluconazole release from all formulations studied here showed in table 2. Well-defined polymeric structure of HPMC and Carbopol permit easier transport of the drug across the concentration gradient created at the membrane compared to other polymers.





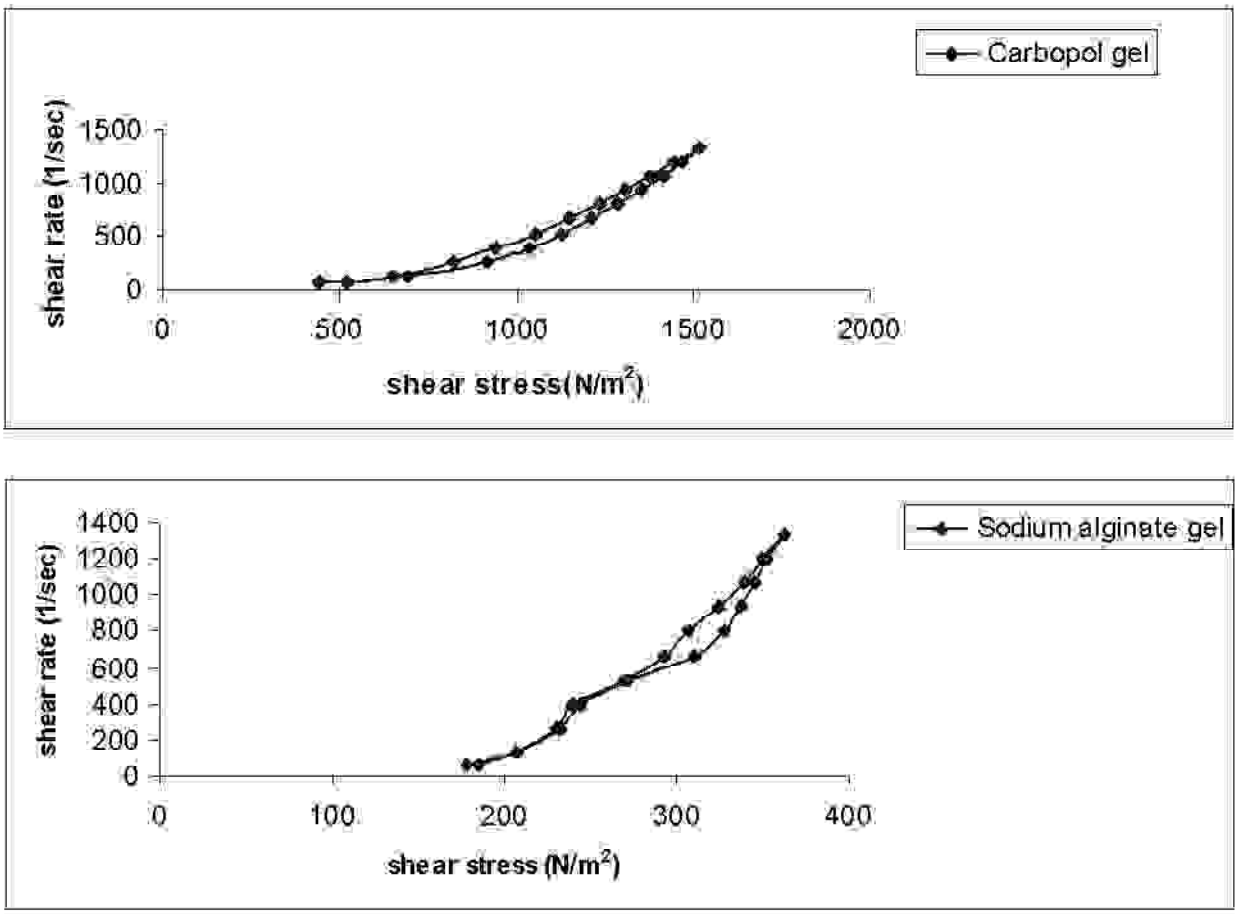


Figure1: Rheogarm of HPMC, Methylcellulose, Carbopol, Sodium alginate gel containing Fluconazole 0.5%w/w.

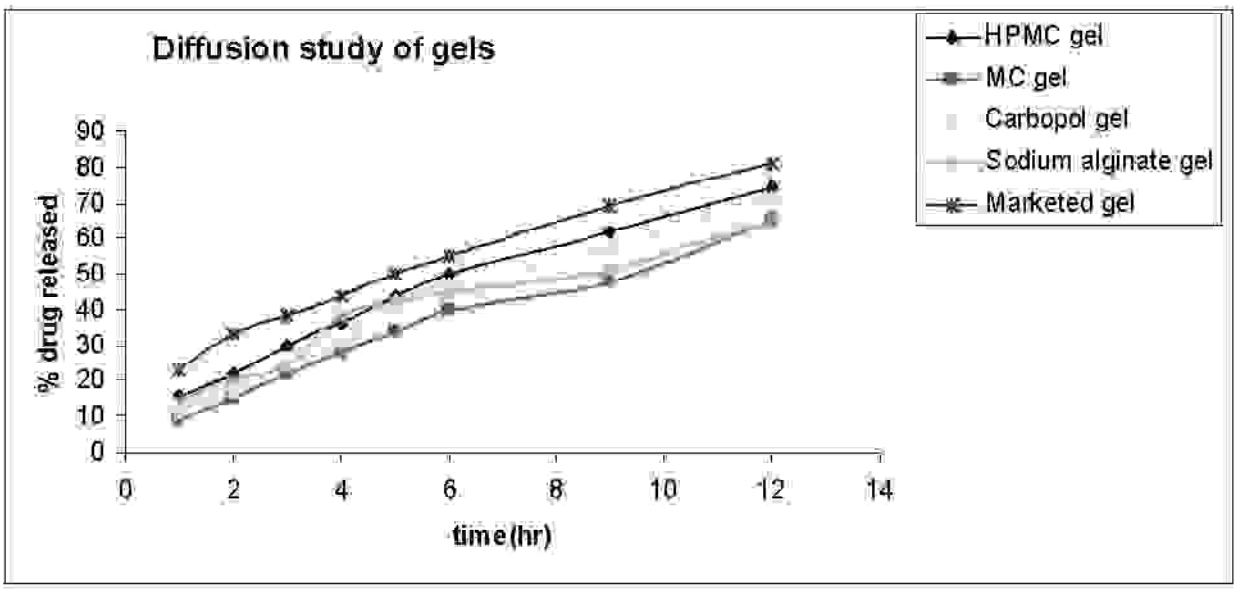


Figure 2: Diffusion profile of Fluconazole from various gel formulations

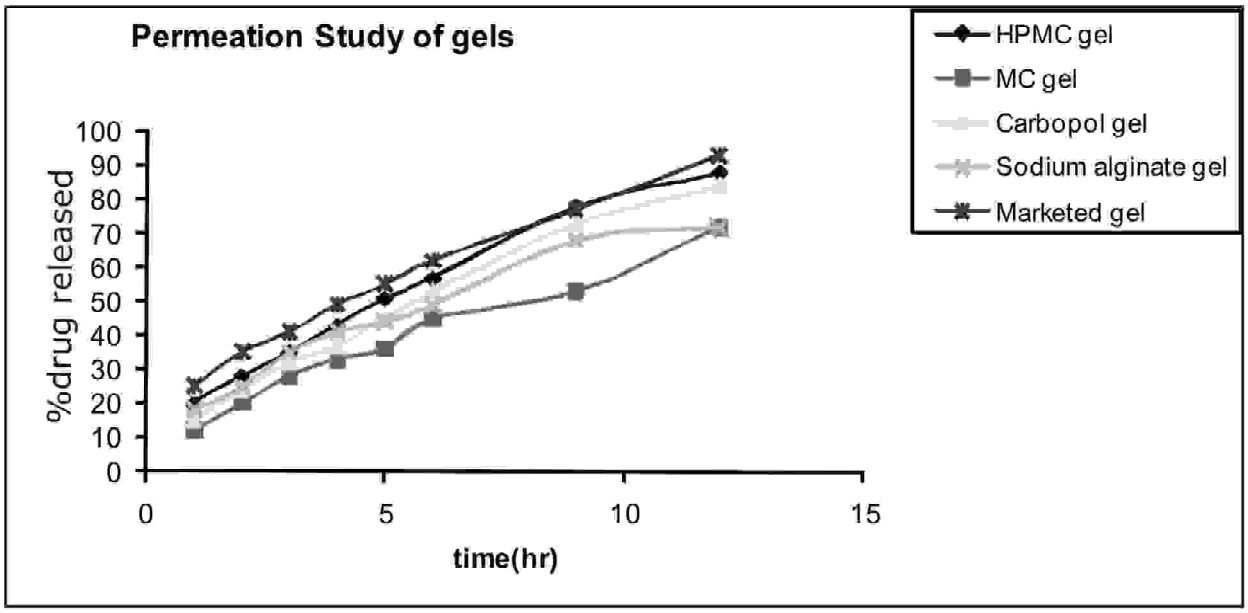


Figure 3: Comparative permeation study of Fluconazole from Gel formulations

Table 1: Formulation of various Fluconazole gels

SR NO	INGREDIENTS	HPMC gel	METHYL CELLULOSE gel	CARBOPOL gel	SODIUM ALGINATE gel
1.	Fluconazole	0.5%	0.5%	0.5%	0.5%
2.	HPMC (4000cps)	2.5%	-	-	-
3.	Methyl Cellulose	-	5%	-	-
4.	Carbopol 934	-	-	1.5%	-
5.	Triethanolamine	-	-	0.9%	-
6.	Sodium Alginate	-	-	-	6%
7.	Calcium Gluconate	-	-	-	0.5%
8.	Ethanol	2.5%	2.5%	2.5%	2.5%
9.	Methyl Paraben	0.15%	0.15%	0.15%	0.15%
10.	PropylParaben	0.05%	0.05%	0.05%	0.05%
11.	Water (qs)	100ml	100ml	100ml	100ml

Table 2: Characteristics of various Fluconazole gel formulation

Sr No.	Formulation	pH	Viscosity (cps)	Spreadibility (g.cm/s)	Drug content (%w/w)	%Drug release after 12hrs (Diffusion study)	%Drug release after 12hrs (Permeation study)	Skin irritation
1.	HPMC gel	7.24	1500	16.30	98.7	74	88	-
2.	MC gel 7.04	1305	25.58	97.2	65	72	-	
3.	Carbopol gel	7.41	1811	14.61	98.4	72	84	-
4.	Sodium alginate gel	7.14	435	25.58	96.9	65	72	-
5.	Marketed gel	7.1	1612	14.80	99.7	81	91	-

The value indicates - no skin irritation

The formulated gels were kept for stability studies. No color fading was observed for all prepared gels. The pH of all formulations were not affected and found to be in the range of 7.00-7.50. The viscosity of all gels was found to be same especially at ambient and 8^0C temperature but at 45^0C slight decrease in viscosity of Sodium alginate and Methyl Cellulose gel was found. The viscosity of HPMC gel and Carbopol gel was found to be satisfactory for stability studies at the selected temperature. The drug content was found to be in the limit 96 –99 % for all gel formulation at all temperature conditions.

CONCLUSION

From above result we can conclude that gel formulation prepared with HPMC and Carbopol 934 showed acceptable physical properties, drug release, in vitro permeation release and which remained unchanged upon storage for 3 months at all temperature conditions. However, the HPMC based gel proved to be the formula of choice, since it showed the highest % drug release and good rheological properties.

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