Section A-Research paper
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Formulation and Evaluation of Topical Gel containing Fluconazole and Clindamycin for treatment of Fungal Infection

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Abstract

Purpose of this research work is to develop Gel for Topical drug delivery system for Antifungal effect. The preparation containing Fluconazole and Clindamycin was selected for preparation. The system delivers the drug at the specified time required by the patient to achieve maximum efficacy and improve drug efficacy with minimal side effects. Fluconazole is an imidazole derivative used for the treatment of local and systemic fungal infection. The oral use of fluconazole is not recommended as it has many side effects. Clindamycin is used primarily to treat anaerobic infections caused by susceptible anaerobic bacteria and having little effect. The present study was designed to formulate and evaluate different formulae of topical gel containing Fixed dose combination of fluconazole with Clindamycin mainly accelerate the anti-fungal effect by acting on fungus as well as reduce development of bacteria's associated with that. 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 color, syneresis, spreadability, pH, drug content and rheological properties. Drug-excipients compatibility studies were confirmed by carrying out DSC and FT-IR. *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 was from F3 (91.3% of drug released after 2 hr). The rheological behavior of the prepared formulae showed shear-thinning flow indicating structural breakdown of the existing intermolecular interactions between polymeric chains.

Keywords: Topical gel, Fixed dose combination, Fluconazole, Clindamycin, anti-fungal, Carbopol 940, Hydroxypropyl methylcellulose E4M, Methyl cellulose, Pectin and Pluronic P407

1. Introduction:

Fungal infection of skin is now-a-days one of the common dermatological problem. The physicians have a wide choice for treatment from solid dosage to semisolid dosage form and to liquid dosage formulation. [1] Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. [2]

Fungal infections traditionally have been divided into two distinct classes: systemic and superficial. Consequently, the major antifungal agents are classified into systemic and topical drugs. Antifungal drugs are classified according to their chemical structure as: polyene antifungals, azole antifungals, allylamine antifungals, echinocandin antifungals and others. [3-4]

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. [5]

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. [6]

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Gels for dermatological use have several favourable properties such as being thixotropic, greaseless, easily spreadable, easily removed, emollient, non-staining, and compatible with several excipients and water soluble or miscible. [8]

Fluconazole is a synthetic antifungal agent belonging to the group of triazole.it is one of the commonly used antifungal agents for most kinds of fungal infections including superficial and invasive fungal infections. Fluconazole differs markedly from other imidazole in its

pharmacokinetic properties. The presence of two triazole rings (bistriazole) makes this compound less lipophilic and more hydrophilic when compared with other azoles antifungal agents. The presence of halogenated phenyl ring increases its antifungal activity. [9-10]

Fluconazole is available commercially as tablets and injections only in spite of its well-known adverse effects including nausea, vomiting, bloating and abdominal discomfort. In order to bypass these disadvantages, the gel formulations have been proposed as topical application.

Clindamycin is an antibiotic medication used for the treatment of a number of bacterial infections, including osteomyelitis (bone) or joint infections, pelvic inflammatory disease, strep throat, pneumonia, acute otitis media (middle ear infections), and endocarditis. It can also be used to treat acne, and some cases of methicillin-resistant Staphylococcus aureus (MRSA). In combination with quinine, it can be used to treat malaria. It is available by mouth, by injection into a vein, and as a cream or a gel to be applied to the skin or in the vagina. [11-12]

The goal of our research to formulate and evaluate various polymers with varying concentrations for the preparation of a safe, effective and stable gel containing Fluconazole and Clindamycin in combination and evaluate the in-vitro performance, stability and also evaluate the in-vitro antifungal activity for prepared formulae. Since no such marketed preparations are available there is a need of advanced delivery system of drug. Therefore, compared with increasing the dose of monotherapy, the use of combination therapy provides better action. Overall, the combination therapy seems to be better than increasing the dose.

Rationale of fixed dose combination:

➢ Fluconazole with Clindamycin mainly accelerate the anti-fungal effect by acting on fungus as well as reduce development of bacteria's associated with that. [13]

➢ Fixed dose combination development to a 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. [14]

2. MATERIALS & METHODS

2.1. Materials. Fluconazole with Clindamycin was a present from the Atra Pharmaceuticals Aurangabad (Maharashtra, India), Carbopol 940, Hydroxypropyl methylcellulose E4M, Methyl cellulose, Pectin and Pluronic P407 was gifts from IPCA Laboratories Ltd. SEZ Pithampur, Indore (M.P., India).

2.2. Preformulation Studies [15]

Organoleptic. The descriptive color, odor, taste & for crystal morphology was determined using a compound microscope.

Melting-point determination. The sample's melting point helps us determining its purity. Melting point was established by filling a closed capillary with drugs & melting it. Temp at which solid drug turns liquid has been studied.

Partition Coefficient. Study measures hydrophobicity & membrane permeability in drug design. Partition coefficient is the ratio between the drug's n-octanol & water concentrations.

$$\mathbf{Po/w = (COil / C\ water)\ equilibrium}$$

2.3. Physicochemical characteristics. Angle of repose, tapped density, bulk density, Carr's index, Hausner's ratio, & blend homogeneity were examined. [16]

Angle of repose. It is obtained when bulk powder is allowed to flow from a fixed height.

$$\mathbf{Angle\ of\ repose = Tan^{-}\ 1\ h/r}$$

Bulk density, is mass/volume. Pouring pre-weighed powder in a graduated cylinder measured bulk density of pure drugs & mixtures & is measured by poured volume & mass of powder.

$$\mathbf{Pb = M\ /Vb}$$

Tapped density. It was calculated by pouring specified quantity of mixed powder in a graduated cylinder & tapping it 100 times until the powder bed volume was minimal.

$$\mathbf{Pt = M\ /\ Vt}$$

Hausner's ratio. It's a basic index that determine powder flow parameters.

Hausner's ratio = *TBD/ LBD ×100*

Carr's index. It's a basic index used to interpret powder flow.

Carr's index = *TBD- LBD/ LBD×100*

2.4. Method of simultaneous equations.

For simultaneous estimation in a drug combination with a fixed dosage. Double distilled water was used to dilute the stock solutions of Fluconazole and Clindamycin to produce separate concentrations of 2–6 g/ml of Fluconazole & 5–15 g/ml of Clindamycin. Two wavelengths, 261 & 210 nm, were chosen from the overlapping spectra to produce a simultaneous equation. At both wavelengths, the absorptivity values of both drugs, E (1%, 1 cm), were calculated. A dilution of 2.5:6.25 g/ml & five binary combination solutions of Fluconazole and Clindamycin were made in ratio of 2:5, which is extremely close to the therapeutic dosage ratio of 2.5:6.25 for the two drugs. Simultaneous equations were solved to estimate the drugs quantitatively.

$$Cx = (A2ay1-A1ay2) / (ax2ay1-ax1ay2) \quad (1)$$

$$Cy = (A1ax2-A2ax1) / (ax2ay1-ax1ay2) \quad (2)$$

Where, Cx is the conc. of Fluconazole & Cy is the conc. of Clindamycin, & A1 & A2 are the mixture's absorbance at 261 & 210 nm, respectively. Similarly, ax1 & ax2, ay1 & ay2 are the absorptivities of x & y at 261 & 210 nm, respectively. [17]

2.5 Preparation of Topical gels

The composition of Fluconazole & Clindamycin topical gel formulae are shown in table. Fluconazole & Clindamycin (1% w/w each) was dissolved in a hot mixture containing propylene glycol (20% w/w)and glycerin (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: Shows composition of Topical Gel (% w/w)

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Fluconazole	1	1	1	1	1	1	1	1	1	1
Clindamycin	1	1	1	1	1	1	1	1	1	1
Carbopol940	**0.5**	**1**	—	—	—	—	—	—	—	—
HPMC	—	—	**1.5**	**2**	—	—	—	—	—	—
Methyl Cellulose	—	—	—	—	**2**	**4**	—	—	—	—
Pectin	—	—	—	—	—	—	**3**	**4**	—	—
PluronicF127	—	—	—	—	—	—	—	—	**15**	**18**
Glycerin	10	10	10	10	10	10	10	10	10	10
Propylene Glycol	20	20	20	20	20	20	20	20	20	20
Methyl Paraben	0.03	0.03	0.03	0.03	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	0.01	0.01	0.01	0.01
Purified water to	100	100	100	100	100	100	100	100	100	100

2.6 Physicochemical Evaluation of Prepared Gels [18]

2.6.1 Drug-Excipients Compatibility Studies

A-Differential scanning calorimetry (DSC)

The DSC studies were performed for the drugs, the polymers and the drug-polymer physical mixtures in the ratio 1:1. The samples (3-4 mg) were inserted in aluminum pan and heated in the rate of 10ºC⁄min, to a temperature of 200ºC using a differential scanning calorimeter (TA-501; shimadzu corporation, Japan).

B- Fourier Transfer Infrared spectrophotometer (FTIR)

The FTIR studies were carried for the drugs, the polymers and the drug-polymer physical mixture in the ratio 1:1 were mixed separately with IR grade KBr in the ratio of (100:1) and corresponding discs were prepared by applying 5.5 metric ton of pressure in a hydraulic press

using FTIR Spectrophotometer. The disks were scanned over a wave number range (4000 - 400cm).

2.6.2 Visual examination

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

2.6.3 Spreadability 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 expected19. Diameters of spreaded circles were measured in cm and were taken as comparative values for spreadability. The results obtained are average of three determinations.

2.6.4 pH determination

The pH of the gels was determined using digital pH meter. The readings were taken for average of 3 times.

2.6.5 Drug Content determination [18]

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 2hr 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, Shimadzu, Japan).

2.6.6 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-52. The apparent viscosity was determined at shear rate 40 sec-1. The flow index was determined by linear regression of the logarithmic form of the following equation:

$$\tau = k\,\gamma\,n \quad \ldots\ldots\ldots\ldots \quad (1)$$

Where "τ" is the shear stress, "γ" is the shear rate, k is the consistency index, and n is the flow index. When the flow is Newtonian n=1, if n>1 or n<1, shear thickening or shear thinning is indicated, respectively. Evaluation was conducted in triplicate.

2.7 *In Vitro* Release Studies [18]

The study was carried out using. One gram of Gel was placed in the watch glass covered with aluminum mesh. The watch glass was then immersed in the vessel containing 500 ml of the release medium, phosphate buffer pH 5.5 at 37ºC ± 0.5 ºC 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 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.

2.8 Drug Release Kinetic Study [19]

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 k0 is the zero – order release rate.

b. First – order equation:

$$In\ (100 - Q) = In\ 100 - k1\ t$$

Where Q is the percent of drug release at time t, and k1 is the first – order release rate constant.

c. Higuchi's equation:

$$Q = k\ t\ 1/2$$

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

2.9 *In-vitro* Drug Diffusion Study [20]

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 ± 0.5ºC. The shafts were rotated at 50 rpm and aliquots each of 3 ml were withdrawn from the release medium at specified time intervals. Withdrawn samples were replaced by equal volumes of fresh release medium. The samples were assayed spectrophotometrically and the concentration of the drug was determined from the previously constructed calibration curve. Each data point represented the average of three determinations. In vitro release studies were recorded for a four hour period. Previous solubility tests were made so as to ensure sink conditions for drug dissolution in the donor medium. The flux, lag time and permeability coefficients of Fluconazole & Clindamycin through synthetic membrane.

3. RESULTS & DISCUSSION

3.1. Preformulation studies

Table2: Resultsof Preformulation studies

Properties	**Results**	
	Fluconazole	**Clindamycin**
Description	Amorphous	CrystallinePowder
Taste	Salty	Slightlybitter
Odor	No Odor	No Odor
Color	White	Almostwhite
MeltingPoint	139°C	143°C
PartitionCoefficient	0.89	0.07

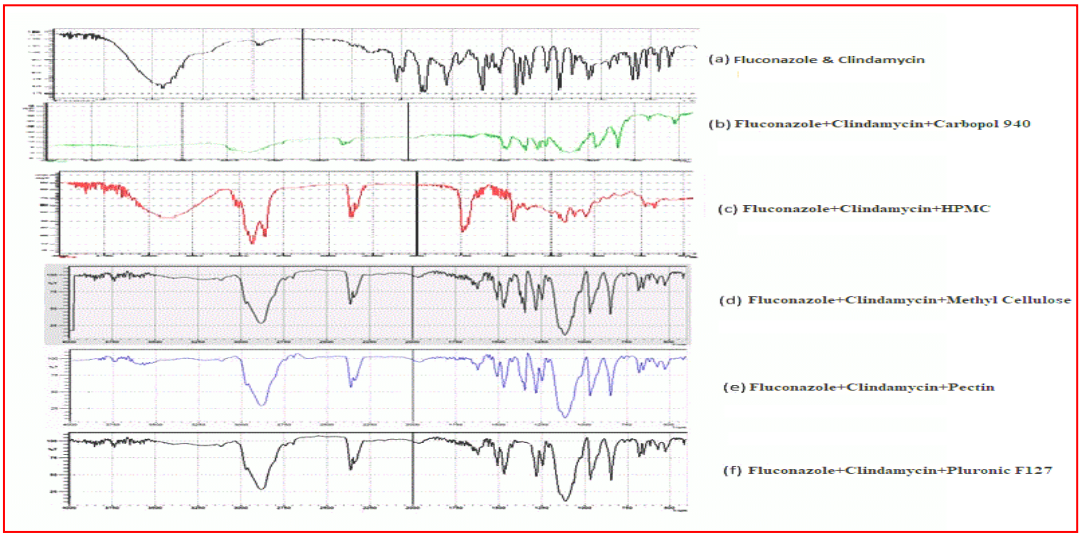
3.1. Drug-recipient mixture results

Table3: Flow properties of Drugs & excipients

Flow property	Physical mixture of Fluconazole, Clindamycin & excipients
Bulk density	0.378g/m3
Tapped density	0.389g/m3
Angle of repose	24.37°
Hausner'sratio	1.33
Carr's index	23.25 %

A. FTIR Study.

Figure shows no drug-polymer interaction. Fluconazole and Clindamycin shows peaks at 1652 cm-1 & 1235 cm-1, respectively. Carbopol 940 maxima were 2959 & 1942 cm-1, HPMC at 1304 & 1482 cm-1, Methyl Cellulose exhibited peaks at 3649 & 2854 cm-1 Pectin at 1443 & 1304 cm-1 and Pluronic F127 at 2342 & 2113 cm-1 respectively. The drug & polymer have no chemical interaction, as revealed spectra. A few bands in the formulation vanished & merged as a result of the cross-linking of polymers. Drugs exhibited spectra at 1652 & 1235 cm-1 peaks, indicating the drug was pure & had not underwent structural alterations.



bFigure 1: IR study of drugs & polymers

B. DSC (Differential Scanning Calorimetry). The DSC Thermogram for Fluconazole, Clindamycin & Physical mixture is shown in Figure. The thermographs produced via DSC study show that melting point of a pure drug is between 110°C & 140°C, whereas that of a formulation is between 204°C & 292°C. A small but noticeable difference exists between the melting points of the pure medication & its preparations. This shows that the drugs remain unreacted even after being formulated. This demonstrates that the drug & polymer have no chemical interactions.

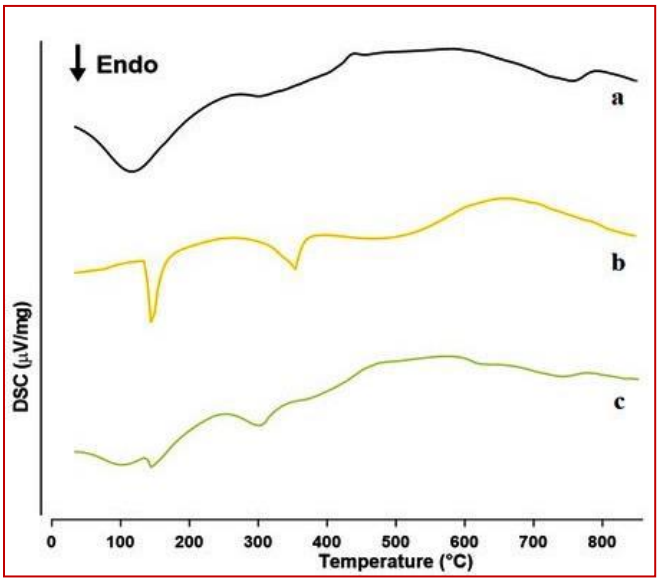


Figure 2: DSC Thermogram for: (a) Clindamycin, (b) fluconazole (c) Physical mixture (Drugs + polymer)

3.3 Evaluation of Topical Gel

3.3.1 Visual examination

The prepared gel formulae were inspected visually for their color and syneresis. The developed preparations were much clear and transparent except pectin gel is buff, opaque. All developed gel formulae showed good homogeneity with absence of lumps and syneresis. Results are shown in table.

3.3.2 Spreadability

The spreadability is very much important as show the behavior of gel comes out from the tube. The values of spreadability shown in table indicate that all the polymers used gave gels

spread by small amount of shear. The diameters of the spreaded circles ranged from 3 cm seen with the Pluronic F127gel and 5 cm seen with carbopol and HPMC gel. Data in table revealed that increasing the concentration of any of the gelling agents was always associated with a decrease in the spreadability as expressed by the lower diameter of the spreaded circle.

3.3.3 pH Determination

The pH values of all developed formulae was in range 5-6 which is considered acceptable to avoid the risk of irritation upon application to the skin.27,28 with the exception of pectin gel;pH was about 3.5; results are tabulated in table.

3.3.4 Drug Content determination

Results of drug content are shown in table. After various formulation of gel the combined drug content of the formulated gel was estimated and the results were in the official limits with range of 9.5 to 9.99 mg/gm gel. The drug content determination also showed that the drug was uniformly distributed throughout the gel.

Table4: Shows the Physical Properties of Topical Gels

Topical Gels	Color	Syneresis	Spreadaility (cm)	pH	Combined Drug content (mg/gm gel)
F1	Shiny transparent	-ve	4.5	6.1	9.55
F2	Shiny transparent	-ve	4	5.99	9.7
F3	transparent	-ve	5	5.60	9.99
F4	transparent	-ve	5	5.67	9.78
F5	Translucent yellowish	-ve	4.5	6.1	9.99
F6	Translucent yellowish	-ve	3.6	6.13	9.7
F7	Opaque, buff	-ve	5	3.6	9.7
F8	Opaque, buff	-ve	3.5	3.7	9.98
F9	transparent	-ve	3.6	6.22	9.93
F10	transparent	-ve	3	6.3	9.89

3.4 Rheological properties of Topical Gels

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.

Table 5: Shows the rheological properties of Fluconazole Topical Gels

Formula	Coefficient of determination (R^2)	Flow Index(n)	Viscosity* (centipoise) (η)	Flow Behavior
F1	0.916	0.2384	1709	Shear thinning
F2	0.9291	0.2350	1918	Shear thinning
F3	0.9976	0.2251	1012	Shear thinning
F4	0.9823	0.21031	1036	Shear thinning
F5	0.908	0.2307	1449	Shear thinning
F6	0.908	0.2307	2083	Shear thinning
F7	0.9304	0.1214	1247	Shear thinning
F8	0.9819	0.1436	2289	Shear thinning
F9	0.9375	0.1390	2441	Shear thinning
F10	0.9459	0.1428	3261	Shear thinning

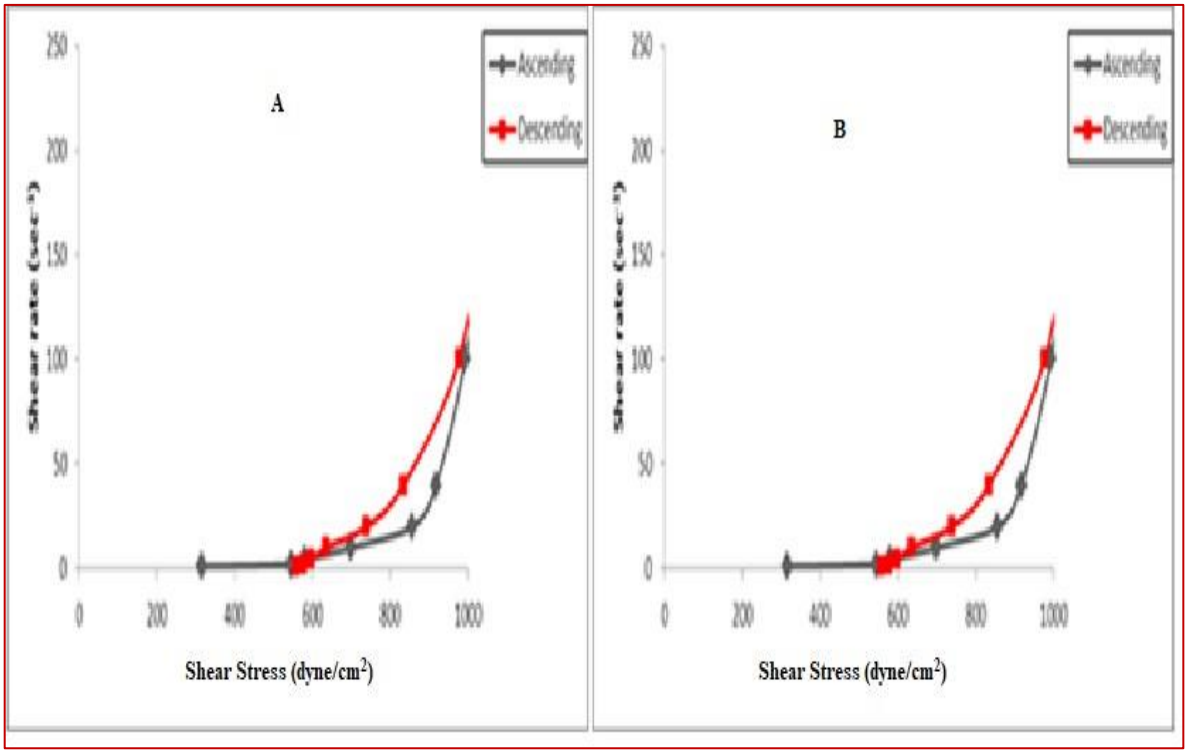


Figure 3: Show rheograms of Carbopo l940 containing Topical Gel(A):F-1,(B):F-2.

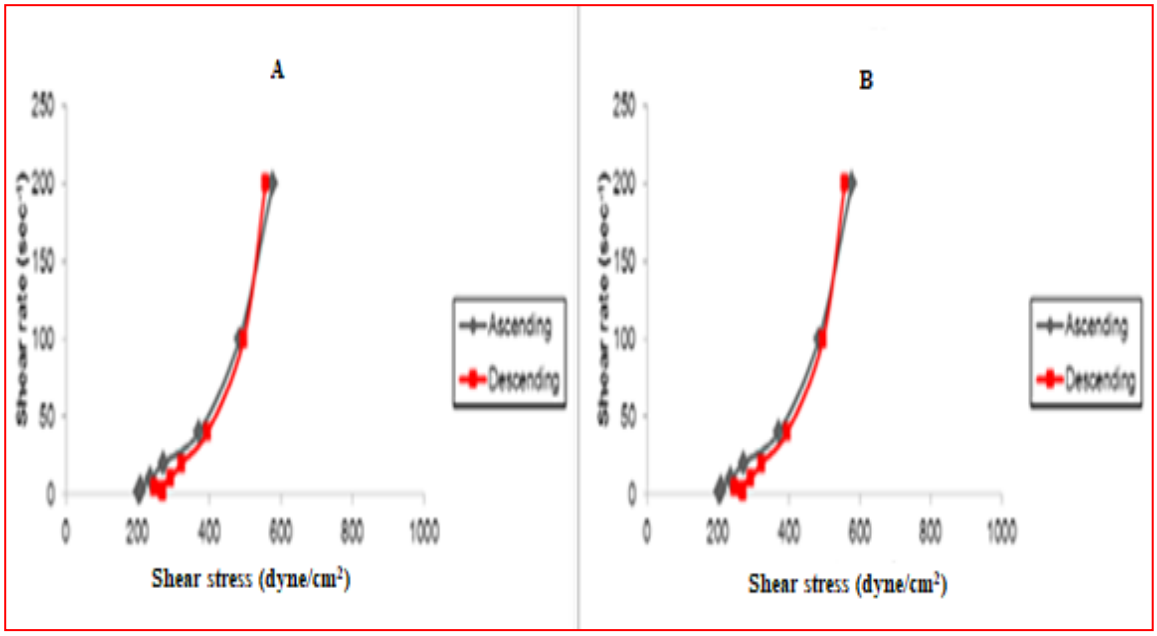


Figure 4: Show rheograms of HPMC containing topical gel (A):F-3,(B):F-4

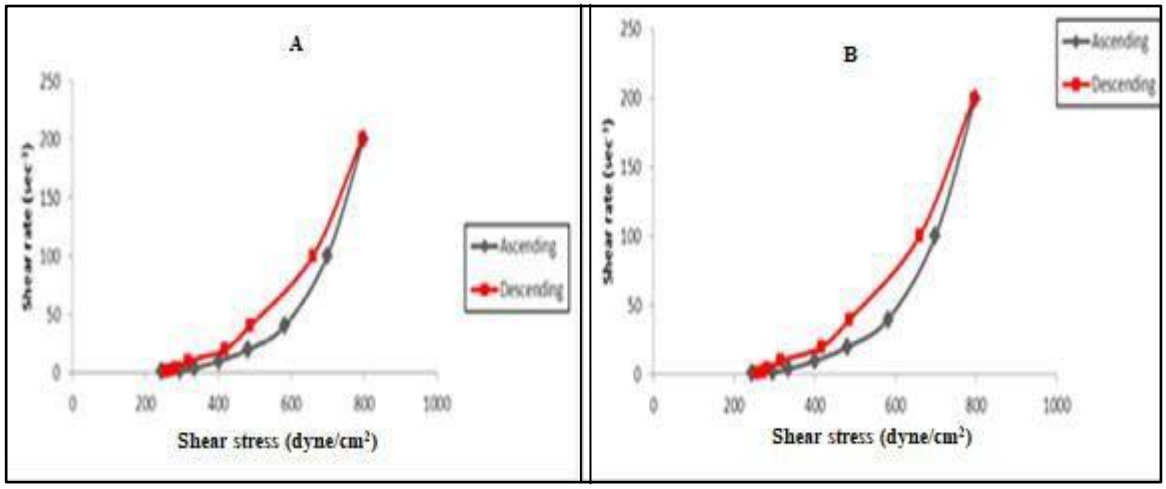


Figure 5: Show rheograms of MC containing topical gel (A): F-5, (B):F-6.

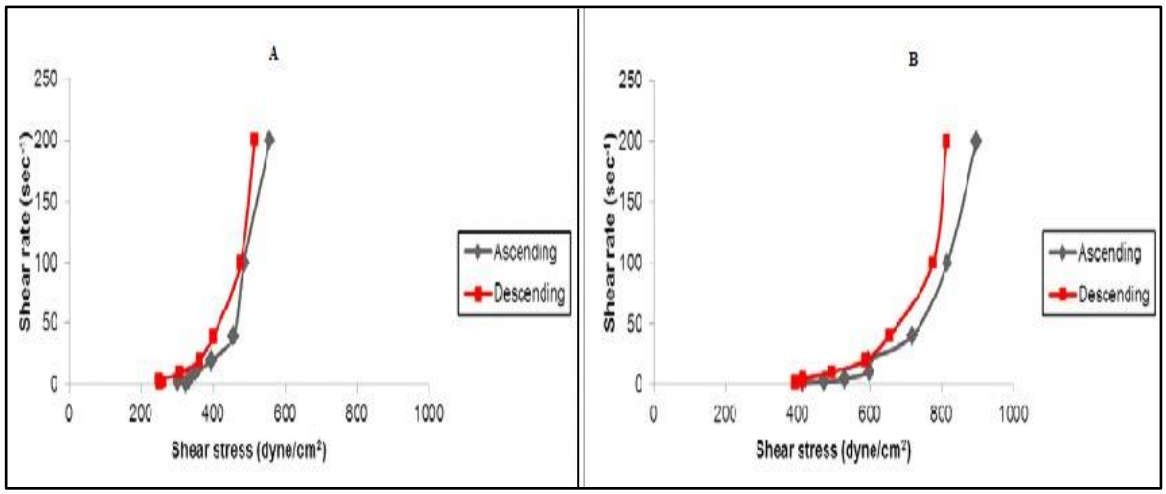


Figure 6: Show rheograms of Pectin containing topical gel (A): F-7,(B):F-8.

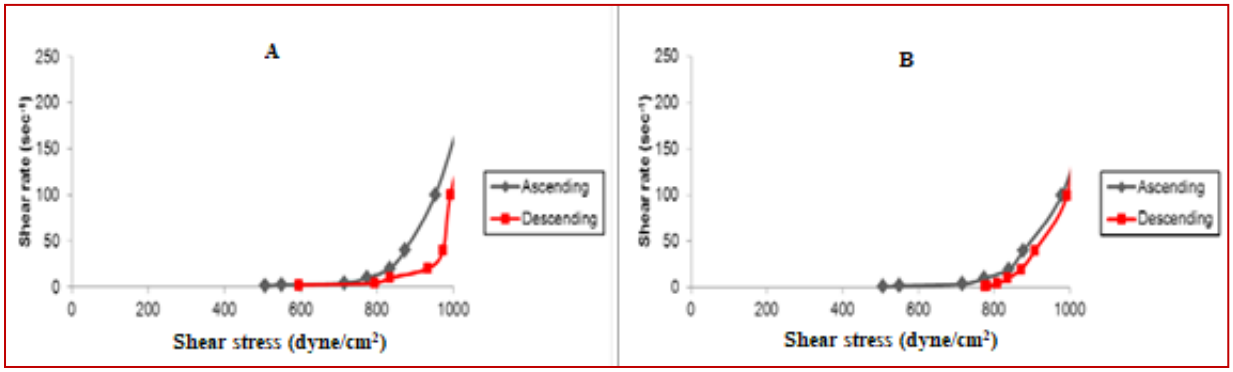


Figure 7: Show rheograms of Pluronic containing topical gel (A): F-9, (B): F-10

In-Vitro Release Studies

The In-Vitro release profile of Topical gel formulae was represented in the Figure. It was observed that the release of the drug from its different formulae can be ranked in the following descending order for Fluconazole: F 3>F 4>F 5>F 7>F 9>F 8>F 1>F 10>F 2>F 6; where the amounts of the drug released after 2 hours were 91.3%, 89.6%, 84.5%, 82.3%, 79.8%, 77.6%, 73.6%, 73%, 69.5% and 58.6% and for Clindamycin F 3>F 4>F 5>F 7>F 9>F 8>F 1>F 10>F 2>F 6; where the amounts of the drug released after 2 hours were 92.3%, 90.2%, 83.4%, 80.1%, 80.8%, 78.4%, 72.4%, 74%, 68.6% and 57.5%respectively. It was observed that the most influenced factor in the drug release is polymer type followed by the concentration of the polymer.

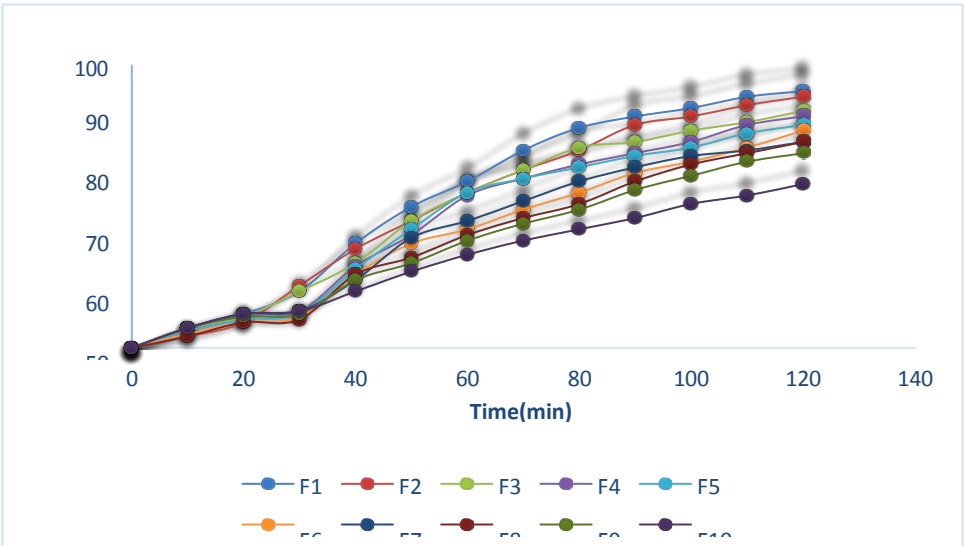


Figure 8: Shows Release profile of Fluconazole from its gel formulae

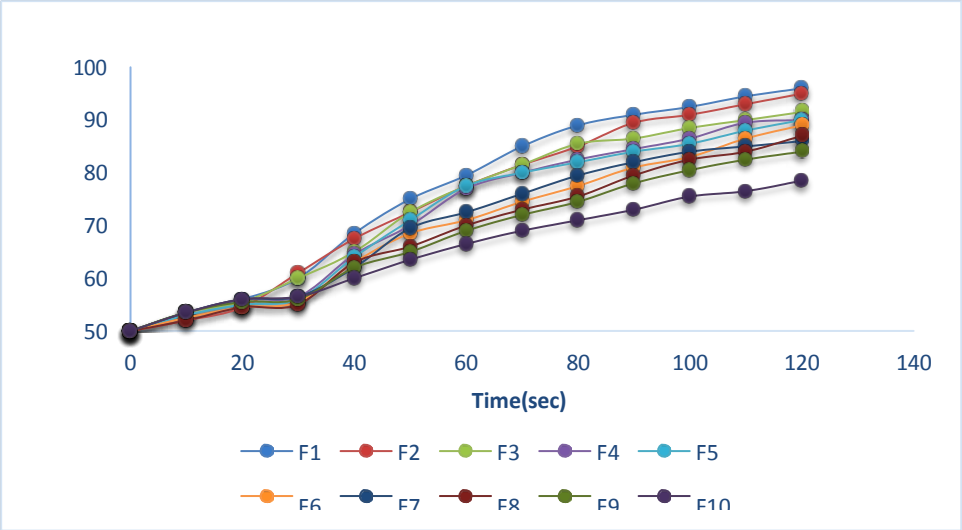


Figure 9: Shows Release profile of Clindamycin from its gel formulae

Drug Release Kinetic Study

The release data analysis was carried out using the various kinetic models i.e using cumulative % drug release vs. time (zero order kinetic model); log cumulative % drug remaining vs. time (first order kinetic model) and cumulative % drug release vs. square root of time (Higuchi model). The R2 values are tabulated in table. All formulae showed best fitting to Higuchi model kinetics.

Table 6: Shows the Kinetic study of the *In vitro* release data of Fluconazole & Clindamycin from its different formulae

Formula	**Correlation Coefficient (R^2)**					
	Zero order		**First order**		**Diffusion**	
	Fluconazole	**Clindamycin**	**Fluconazole**	**Clindamycin**	**Fluconazole**	**Clindamycin**
F1	0.9339	0.9456	0.9896	0.9906	0.9929	0.9949
F2	0.954	0.952	0.9958	0.9842	0.9960	0.9991
F3	0.8727	0.8711	0.9722	0.9769	0.9938	0.9968
F4	0.9268	0.9201	0.9928	0.9889	0.9994	0.9982
F5	0.9651	0.9623	0.9893	0.9897	0.9975	0.9887
F6	0.903	0.910	0.9438	0.9269	0.9649	0.9786
F7	0.7823	0.7936	0.9255	0.9301	0.9255	0.9352

F8	0.9666	0.9768	0.9876	0.9799	0.9950	0.9889
F9	0.9593	0.9687	0.9905	0.9899	0.9964	0.9992
F10	0.9833	0.9910	0.9774	0.9879	0.9935	0.9854

In-vitro Drug Diffusion Study

The results of in vitro permeation studies of topical gel formulae across cellulose membrane are shown in table. The cumulative amount of Fluconazole and Clindamycin released from all gel formulae show a linear relationship with the square root of time (r >0.9). The cumulative amounts permeated at 4 hrs were 220.63, 246.2, 174.23, 243.8, and 144.44µg/cm2/h for F1, F3, F5, F7, and F9, respectively. The vehicle composition can affect drug release and skin permeability properties. These results suggest that F3 is effective for topical application as highest percentage of the applied drug permeated through the human epidermis after 4 hours.

Table 7: Show the In vitro Drug Diffusion Study of the Selected Topical Gels

Topical gel	**Js(µg $cm^{-2}hr^{-1}$)**	**P(cm hr^{-1})**	**K**	**r**
F1	220.63	0.022	36.94	0.9475
F3	246.37	0.024	146.53	0.9999
F5	174.23	0.017	6.76	0.99999
F7	243.83	0.024	61.66	0.9865
F9	144.44	0.004	-428.71	0.9945

4. Conclusion

On the basis of the previous findings we can concluded that Topical gel was successfully incorporated into the different topical gel preparations. From among all the developed formulation the formula F 3 shows good spreadability, viscosity, drug release and antifungal effect. Therefore, it was concluded that our formulae could be very promising topical alternative for the treatment of skin fungal infections. However, further preclinical, *In-vivo* and stability studies are required.

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