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FORMULATION AND IN VITRO EVALUATION OF HYALURONIC ACID BASED HYDROGEL OF FLUCONAZOLE FOR TOPICAL DRUG DELIVERY

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ABSTRACT

The present investigation is made to design, prepare Hydrogels containing Fluconazole with hyaluronic acid as a carrier, the hydrogels prepared are subjected to extensive rheological evaluation, drug content, pH, homogeneity, clarity, extrudability, Spreadability, antifungal activity and drug diffusion study across artificial membrane (cellophane membrane). The influence of permeation enhancers like Oleic Acid, Propylene Glycol, Capric Acid, Caprylic Acid, PEG-400 and PEG-600 on artificial membrane permeation are also studied. The major outcomes of the research are as follows. Hydrogels prepared using HA revealed a pH of 6.5 - 7.0. Since HA is a component of the human skin no hypersensitivity reactions can be expected when used as a carrier in preparation of topical hydrogels. Rheological evaluation studies indicated there is no significant change in the viscosity of the formulation. The prepared HA hydrogels had a greater rate of permeation as compared with the marketed formulation (FLUCOS GEL, Cosme). From the results of the experiment we can expect a superior onset of therapeutic action.

KEYWORDS

Hyaluronic acid, Hydrogels, Permeation enhancers, *In-vitro* diffusion and Antifungal activity.

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INTRODUCTION

The topical drug delivery systems are self-contained, discrete dosage forms which when applied to intact skin deliver the drug through the skin at a controlled rate to the systemic circulation. In modern days, even many of the delivery systems was developed, still oral route is the most commonly selected route by the patients and the researchers for the development of drug delivery systems through this way. While this has the notable advantage of easy administration, it also has significant drawbacks namely poor bioavailability

due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes leading to a need for high or frequent dosing, which can be both cost prohibitive and inconvenient. Hence there is a need to avoid these difficulties and to develop new drug delivery systems for the delivery of drug through other than oral route, which can have maximum utilization of drug, better therapeutic effect and safety of drug by more precise (from site specific delivery). Hence, we considered one of the methods which most often utilized is topical drug delivery by hydrogels which transports therapeutic substances through the skin for systemic effect.

The success of topical delivery depends on the ability of the drug to permeate the skin in sufficient quantities to achieve its desired therapeutic effects, because. The stratum corneum provides the greatest resistance to penetration and it is the rate-limiting step in Percutaneous absorption which involves the passage of drug into stratum corneum followed by diffusion into epidermis, dermis, blood capillaries from the surface of skin, which depends on many factors like concentration gradient, partition coefficient of drug etc. the present study was developed by considering the different penetration enhancers with hyaluronic acid as carrier for the better penetration of drug into skin and systemic circulation[1].

MATERIAL AND METHODS

Materials

Fluconazole was the gifted from Glenmark pharmaceuticals, Goa. Sodium hyaluronate was obtained from Kumar Organic Products Pvt. Ltd, Bangalore. Oleic acid, Polyethylene glycol (PEG-400), Polyethylene glycol (PEG-600), Glycerine, Ethanol were obtained from Merck Ltd, Mumbai. Propylene glycol, Capric acid, Caprylic acid were obtained from Lobachemie Pvt.ltd, Mumbai. Sabouraud dextrose medium was obtained from Labsol Enterprises, Mumbai. Deionised water was done and used by Milli-Q water purification system Millipore, USA.

METHODS

Formulation Details

Preparation of Fluconazole Hyaluronic acid (F-HA) hydrogels

A quantity of HA, permeation enhancer and glycerin are added as specified in Table No.3 and mixed in about 10 ml of deionized water using a magnetic stirrer at room temperature for 30 minutes to obtain a homogenous gel. Fluconazole was then dissolved in 1 ml of ethanol and then dissolved in deionized water. This ethanolic solution of the drug is then added to the prepared gel and mixed using a magnetic stirrer until homogeneity is achieved. Stirring speed is adjusted to minimize the air entrapment in the gel and deionized water is added to adjust the weight of the gel to 10gm. The final gel formulation contained Fluconazole equivalent to 1% w/w. The prepared gel is then transferred into 20 ml polypropylene centrifuge tubes and preserved at 24ºC and 60% Relative humidity until further use.

Characterization Of F-Ha Hydrogels[2,3,4]

Gels were evaluated for their clarity, pH, viscosity, Spreadability, skin irritation test, anti-fungal activity, drug content, *in vitro* diffusion studies and *in vivo* studies by using standard procedure.

Clarity

The clarity of various formulations was determined by visual inspection under black and white background and it was graded as follows; turbid: +, clear: ++, very clear (glassy): +++.

pH

2.5 grams of gel was accurately weighed and dispersed in 25 ml of distilled water. The pH of dispersion was measured by using digital pH meter (LABINDIA).

Homogeneity

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container for their appearance and presence of any aggregate.

Spread ability

The Spreadability of the gel formulation was determined, by measuring diameter of 1 gm gel between horizontal plates (20×20 cm^2) after 1 minute. The standardized weight tied on the upper plate was 250 gm. glass slide apparatus. The time

required to separate the two slides, i.e. the time in which the upper glass slide moves over the lower plates was taken as measure of Spread ability (S).

Spreadability was calculated by using the formula:

S = ML/T

Where, S = Spreadability; M = weight tied to upper slide; L = length moved on the glass slide

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

Viscosity measurement

Brook field viscometer is used for the studies. Rheological observations are studied at HA concentrations ranging from 0.5% - 2.0% w/w. 1.0 g of the gel containing HA at 2.5% w/w is taken and the viscometer is dipped into the gel till the notch on the spindle touched the gel surface. The speed of the spindle is adjusted to 5.0 rpm and dial reading is recorded until 2 consecutive similar readings are occurred. Similarly dial readings are recorded at 10.0, 20.0, 40.0, 50.0 and up to 100 rpm. As soon the sample is sheared at the highest rate, another set of dial reading are noted by reducing the spindle rotation in the decreasing order to pool the data on the down curve. Rheograms are constructed by plotting the dial readings on the X-axis and rpm values along the Y-axis.

Drug content

1 gm of F-HA hydrogel equivalent to 10 mg of drug was dissolved in 100 ml of phosphate buffer pH-6.8. The volumetric flask containing gel solution was shaken for 2 hr. on mechanical shaker in order to get complete solubility of drug. This solution was filtered and estimated spectrophotometrically at 260 nm.

Extrudability

The extrude ability test was carried out by using Pfizer hardness tester. A 10gm of gel was filled in aluminum tube. The plunger was adjusted to hold the tube properly. The pressure of 1kg/cm^2 was applied for 30 sec. The quantity of gel extruded was weighed. The procedure was repeated at three equidistance places of the tube. Test was carried out in triplicates.

***In-vitro* Diffusion Studies**

The artificial membrane (cellophane membrane) was taken for the study. 1gm of gel was applied uniformly to cellophane membrane. The artificial membrane was mounted between the compartments of the Franz diffusion cell with gel applied side facing the donor compartment. Reservoir compartment was filled with 25 ml phosphate buffer of pH 6.8. The study was carried out at 37 ± 1°C and speed was adjusted until the vortex touches the artificial membrane and it is carried out for 6 hrs. 2 ml of sample was withdrawn from reservoir compartment at specified intervals and absorbance was measured spectrophotometrically at 260nm. Each time the reservoir compartment was replenished with the 2ml volume of phosphate buffer pH 6.8 solution to maintain constant volume. And this data was subjected to different drug release kinetic study using following plots

Data Analysis (Curve fitting analysis)

The results of in vitro diffusion profiles obtained for all the FHA-Hydrogel formulations were fitted into four models of data treatment as follows:

1. Cumulative percent drug diffused versus time (zero-order kinetic model).
2. Log cumulative percent drug remaining versus time. (First-order kinetic model).
3. Cumulative percent drug diffused versus square root of time (Higuchi's model).
4. Log cumulative percent drug diffused versus log time (Korsmeyer-Peppas equation).

Anti-fungal studies[5]

Weigh 16.25 gm of sabouraud dextrose agar was transferred in a 500 ml of conical flask and 250 ml of purified water and some amount of heat is applied to dissolve it completely. Sterilized for 15 min at 121°C at 15 lb pressure in autoclave for about 20 min. Then cooled it at room temperature and the fungal strain (*Candidaalbicans)* was dispersed in the medium and then the medium was poured it in to the three Petridish and allowed it to coolfor some time at room temperature until it forms solidifies at room temperature and then the three cups are bored in each Petri dish with the help of sterile steel bore of 6 mm and calculated concentration of the standard drug (Fluconazole), gel formulation (F5) and placebo gel were placed in the bores and incubated the Petri plates for 72 h at 37°C in incubators. Then calculate the radius of the zone of inhibition.

RESULTS AND DISCUSSION

Pre-formulation studies

Melting Point

The melting point of Fluconazole was found to be of 140°C.

Standard Calibration Curve for Fluconazole

Standard curve of Fluconazole was determined by plotting absorbance (nm) verses concentration (µg/ml) at 260nm and it follows beer's law. The results were obtained are tabulated below.

Characteristic Peaks of Drugs in FTIR Spectra's

FT-IR spectra of pure Fluconazole and its physical mixtures used in this study. The study showed that there was no major change in the position of peak obtained in the drug alone and in a mixture of drug with excipients, which shows that there was no interaction between drug and excipients. The characteristic peak of -OH group at 3511.96 cm^{-1}, aromatic -CH group at 3024.56 cm^{-1} and - C = N group at 1589.10 present in the entire spectrum indicates the stable structure of Fluconazole in solid admixture.

Post Formulation Studies

Evaluation of Gels

Clarity

All developed formulations of Fluconazole hyaluronic acid (F-HA) hydrogels (F1-F3) with oleic acid as penetration enhancer were found to be white, translucent and (F4-F18) formulations were found to be sparkling and transparent, and marketed gel is white viscous and translucent. All gels were free from presence of particles (shown in Table No.6).

pH

The pH value of all developed formulations of (F-HA) hydrogels (F1-F18) were in the range of 6.5 - 7.0, and marketed gel (Flucos-cosme) was 6.9 (shown in Table No.6). Our HA gel formulations reported a slightly acidic pH value. This may be attributed to the acidity of ethanol used in our formulation.

Homogeneity

All developed (F1-F18) and marketed gel showed good homogeneity with absence of lumps. The developed preparations (F1-F3) were white, translucent and remaining formulations (F4-F18) were much clear and transparent.

Spreadability

The value of spreadability indicates that the gel is easily spreadable by small amount of shear. Spreadability of all formulated gels (F1-F18) were in the range 18.07-27.27 g.cm/sec, whereas marketed gel spreadability was found to be 21.32 g.cm/sec, indicating Spreadability of formulated F-HA hydrogels were good as compared to marketed gel. (Shown in Table No.6).

Extrudability

The extrusion of the gel from the tube is an important during its application and inpatient acceptance. Gels with high consistency may not extrude from tube whereas, low viscous gels may flow quickly, and hence suitable consistency is required in order to extrude the gel from the tube. Extrudability of F-HA hydrogel formulations was found to be good and comparable with marketed gel. (Shown in Table No.6).

Drug content

The percentage drug content of all prepared gel formulations was found to be in the range of 97.71 - 101.46%, whereas the drug content of marketed gel was 98.08%. The percentage drug content of formulations was found satisfactory. Hence methods adopted for gels formulations were found suitable (shown in Table No.6).

Rheological Studies / Viscosity measurements

The viscosity of various formulated Fluconazole gels was measured using a Brook field viscometer. The rheological behavior of all formulated gels systems was studied. In gel system, consistency depends on the ratio of solid fraction, which produces the structure to liquid fraction. Brook field viscometer was used for the studies. Rheological observations were studied at HA concentrations ranging from 0.5 % - 2.0 % w/w.

1.0 g of the gel containing HA at 2.5 %w/w was taken and dipped into the gel till the notch on the spindle touched the gel surface. This spindle was rotated at 5.0 rpm, and dial reading was recorded until 2 consecutive similar readings were obtained. Similarly dial readings were recorded at 10.0, 20.0, 40.0, 50.0 and up to 100 rpm. As soon the sample was sheared at the highest rate, another set of dial reading were recorded by reducing the spindle rotation in the decreasing order to the pool the data

on the down curve. Rheograms were constructed by plotting the dial readings on the X-axis and rpm values along the Y-axis. A graphical representation of the shear viscosity versus shear rate at 37°C (human body temperature) for solutions of HA at different concentrations was shown in Figure No.4. From the graph, it is clearly indicating that Newtonian behaviour is visible at low shear rates followed by shear thinning at higher shear.

A strong rise in the η_{rel} ($\eta_{rel} = \eta_{sample}/ \eta_{water}$) with increasing HA concentrations is observed at 40°C (Figure No.6). The samples were re-analyzed after cooling to 25°C. There is no apparent change in the η_{rel} due to temperature.

This suggests that as the polymer concentration increases, the growth of entanglements creates a strong network that is not substantially deformed or reorganized.

Comparative evaluation properties of the gels

***In-vitro* diffusion studies**

The diffused of Fluconazole from the F-HA hydrogels was studied in 25ml of phosphate buffer pH-6.8 as dissolution medium using a Franz diffusion cell assembly at 37±0.5°C, with a fixed rpm until vortex touches the membrane. Drug content was determined by UV/visible spectrophotometer, UV-3000 LABINDIA, UV-win software (version - 5.2.0.1104) at 260nm. Diffusion studies were performed for a period of six hours. Cumulative percentage of drug diffused was calculated using an equation obtained from the standard curve.

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) , log amount of fraction diffused vs. log time (Krosmeyer Peppas model). R^2 values for all models and slope for Krosmeyer Peppas model are tabulated.

The curve fitting results of the release rate profiles of the prepared formulations are shown in the Table No.6 which gave an idea on the release rate and mechanism of release. The drug release mechanism from all the formulations was best explained by first order equation, as plots showed the maximum linearity (r^2=0.904). It indicates that the rate of drug release is concentration dependent. Even the innovators product (FLUCOS) was found to be follow the same pattern (r^2=0.872) for first order equation. Plots of amount of drug diffused vs. square root of time were found to be linear in all cases indicating that the drug diffusion from the prepared fluconazole hyaluronic acid hydrogels might be of diffusion type as proposed by higuchi.

To further evaluate the drug release mechanism, diffusion data was fitted into Korsmeyer-Peppas equation, the release exponent 'n' values from (0.475 to 0.812) indicating that the release mechanism is anomalous or non-Fickian diffusion. It can be interfered that the release was dependent on diffusion of drug through the membranes.

Among all the formulations, FHA hydrogels with propylene glycol concentration (5.0 % w/w) in F5 indicating 60% of drug release in 6hrs than compared to others, whereas, Marketed Formulation (FLUCOS) showed 27.6 % of drug release. Hence F5 was considered as the best.

Antifungal activity

The incubated Petri plates were taken out and the zone of inhibition was observed for the placebo gel, hydrogel formulation (F5) and calculated concentration of the standard drug (Fluconazole), then the radius of zone of inhibition was measured and tabulated.

Table No.1: Composition of the F-HA hydrogels prepared by using various permeation enhancers

(weights in mg for 10 grams of gel)									
	Hyaluronic acid	**Oleic acid**	**Propylene glycol**	**Capric acid**	**Caprylic acid**	**PEG 400**	**PEG -600**	**Glycerin**	**Drug equv'' to 1% w/w dissolved in 1ml of Ethanol**
F1	250	250	-	-	-	-	-	0.5 ml	10
F2	250	500	-	-	-	-	-	0.5 ml	10
F3	250	750	-	-	-	-	-	0.5 ml	10
F4	250	-	250	-	-	-	-	0.5 ml	10
F5	250	-	500	-	-	-	-	0.5 ml	10
F6	250	-	750	-	-	-	-	0.5 ml	10
F7	250	-	-	250	-	-	-	0.5 ml	10
F8	250	-	-	500	-	-	-	0.5 ml	10
F9	250	-	-	750	-	-	-	0.5 ml	10
F10	250	-	-	-	250	-	-	0.5 ml	10
F11	250	-	-	-	500	-	-	0.5 ml	10
F12	250	-	-	-	750	-	-	0.5 ml	10
F13	250	-	-	-	-	250	-	0.5 ml	10
F14	250	-	-	-	-	500	-	0.5 ml	10
F15	250	-	-	-	-	750	-	0.5 ml	10
F16	250	-	-	-	-	-	250	0.5 ml	10
F17	250	-	-	-	-	-	500	0.5 ml	10
F18	250	-	-	-	-	-	750	0.5 ml	10

Table No.2: Standard calibration curve of Fluconazole

S.No	**Concentration (µg/ml)**	**Absorbance (260 nm)**
1	0	0.000
2	10	0.147
3	20	0.278
4	30	0.416
5	40	0.534
6	50	0.672

Table No.3: Results of drug excipients compatibility studies

S.No	**Description of Functional Group**	**Peaks obtained in the drug Wave in cm^{-1}**	**Peaks obtained in the physical mixture Wave in cm^{-1}**
1	OH Stretching	3511.96	3576.09
2	CH Stretching	2848.41	2935.81
3	CH (Aromatic Stretching)	3014.83	3024.56
4	C = N Stretch	1589.10	1599.75
5	CH (Aromatic bending)	837.33	832.58
6	C - F Stretch	892.04	880.57

Table No.4: Shear rate dependency of the viscosity at 25°C

S.No	Rate of shear (rpm)	Viscosity (cps)
1	5	10254
2	10	10120
3	20	9654
4	40	9014
5	50	8650
6	60	7750
7	80	6950
8	100	4965

Table No.5: Concentration dependence of the relative viscosity at a low shear rate for HA

S.No	Concentration (% w/w)	relative viscosity	Log Relative Viscosity
1	0.5	10254.0	4.010893313
2	1.0	12565.0	4.099162493
3	1.5	35465.0	4.549799964
4	2.0	105040.0	5.021354713

Table No.6: Comparative evaluation properties of the gels

S.No	Clarity	pH	Homo geneity	Spread ability (g.cm/sec)	Extrud ability	% Drug Content
F1	+ +	6.9	Good	21.04	+ +	99.57
F2	+ +	6.9	Good	18.79	+ +	100.04
F3	+ +	7.0	Good	22.40	+ +	98.74
F4	+ + +	6.9	Good	20.55	+ +	98.18
F5	+ + +	6.9	Good	22.39	+ +	102.2
F6	+ + +	6.5	Good	18.99	+ +	98.09
F7	+ + +	6.5	Good	22.78	+ +	101.02
F8	+ + +	6.7	Good	27.27	+ +	101.00
F9	+ + +	6.5	Good	18.20	+ +	97.71
F10	+ + +	7.0	Good	18.07	+ +	99.27
F11	+ + +	7.0	Good	22.06	+ +	101.01
F12	+ + +	7.0	Good	20.68	+ +	101.46
F13	+ + +	6.7	Good	23.42	+ +	98.86
F14	+ + +	6.9	Good	21.97	+ +	98.24
F15	+ + +	6.7	Good	25.96	+ +	98.77
F16	+ + +	7.0	Good	23.16	+ +	101.02
F17	+ + +	7.0	Good	21.42	+ +	100.06
F18	+ + +	6.9	Good	20.99	+ +	99.82
Marketed	+ +	6.9	Good	21.32	+ +	98.05

Table No.7: Comparative *in vitro* drug diffusion data

S.No	Formulations	*IN VITRO* % DRUG DIFFUSED							
		TIME IN MINUTES							
		30	60	90	120	180	240	300	360
1	F1	6.58	13.2	19.0	20.7	21.4	22.6	23.6	25.1
2	F2	29.6	34.1	36.1	36.5	37.2	37.7	38.8	43.6
3	F3	33.6	40.0	41.8	45.9	47.8	49.1	51.4	55.5
4	F4	25.1	29.5	36.1	36.4	36.7	37.3	39.1	46.2
5	F5	37.7	40.8	43.1	45.5	48.6	55.9	59.3	60.0
6	F6	19.4	24.6	26.4	26.8	27.3	28.1	29.3	29.8
7	F7	12.2	22.4	25.6	26.1	27.6	27.9	28.4	30.8
8	F8	13.6	24.7	26.9	28.4	30.2	31.4	33.1	34.3
9	F9	11.4	16.1	24.4	30.3	33.1	34.2	34.7	38.9
10	F10	9.87	10.2	12.2	13.3	14.9	16.5	22.6	28.8
11	F11	19.5	20.0	21.1	22.5	23.3	25.4	25.9	31.8
12	F12	29.8	30.2	30.4	31.6	31.7	31.9	32.1	38.2
13	F13	19.0	19.4	20.3	20.6	21.3	21.6	21.8	22.3
14	F14	14.0	19.8	22.2	30.3	31.6	33.7	40.6	41.6
15	F15	3.53	7.6	9.0	12.3	12.7	13.2	13.8	14.2
16	F16	21.6	23.1	23.6	24.8	25.1	27.2	28.5	28.8
17	F17	21.9	22.2	22.6	22.9	23.4	23.7	25.0	31.8
18	F18	20.9	22.9	23.2	23.9	24.1	24.9	25.6	27.4
19	F Marketed	9.7	10.5	11.5	12.1	13.3	15.3	21.1	27.6

Table No.8: Comparative regression values for different kinetic model plots

S.No	Formulations	Zero order	First order	Higuchi	Korsmeyer Peppas	
		R^2	R^2	R^2	N	R^2
1	F1	0.569	0.737	0.903	0.78	0.401
2	F2	0.0454	0.516	0.718	0.55	0.177
3	F3	0.711	0.682	0.822	0.63	0.175
4	F4	0.581	0.656	0.834	0.62	0.190
5	F5	0.640	0.779	0.865	0.66	0.181
6	F6	0.464	0.499	0.739	0.53	0.170
7	F7	0.582	0.615	0.829	0.66	0.261
8	F8	0.631	0.676	0.868	0.69	0.264
9	F9	0.782	0.824	0.942	0.81	0.373
10	F10	0.895	0.904	0.914	0.69	0.368
11	F11	0.611	0.665	0.823	0.54	0.186
12	F12	0.379	0.420	0.628	0.50	0.126
13	F13	0.344	0.359	0.615	0.63	0.130
14	F14	0.844	0.895	0.977	0.80	0.339
15	F15	0.737	0.748	0.916	0.75	0.507
16	F16	0.468	0.508	0.731	0.50	0.154
17	F17	0.477	0.499	0.698	0.48	0.146
18	F18	0.404	0.514	0.670	0.47	0.141
19	FM	0.516	0.516	0.718	0.66	0.350

Table No.9: Antifungal studies of optimized hydrogel formulation

S.No	Formulation	Zone of inhibition (mm^2)
1	Placebo gel	0
2	F5	6.8
3	Standard drug	7.7

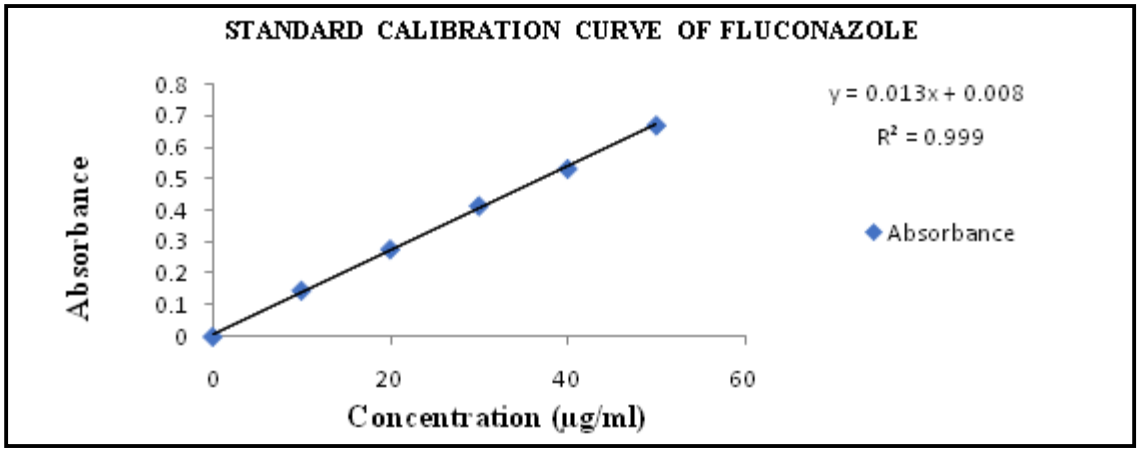

Figure No.1: Standard Calibration Curve of Fluconazole

IR Spectra's

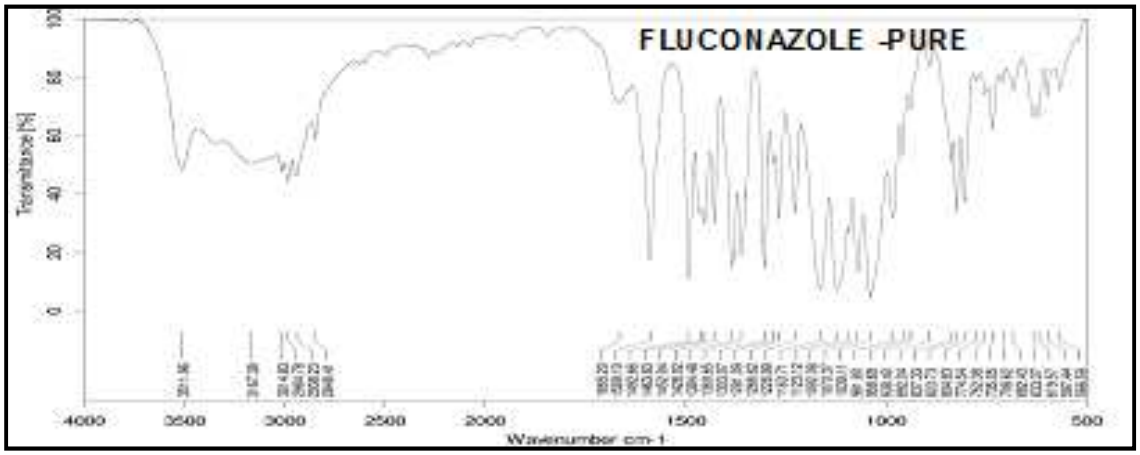

Figure No.2: FT-IR Spectra of Pure Fluconazole

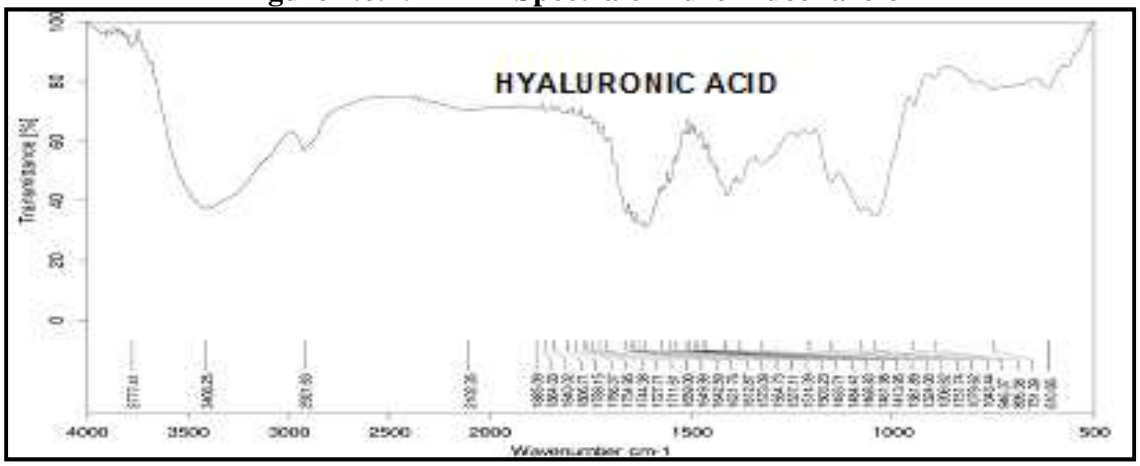

Figure No.3: FT-IR Spectra of Hyaluronic acid

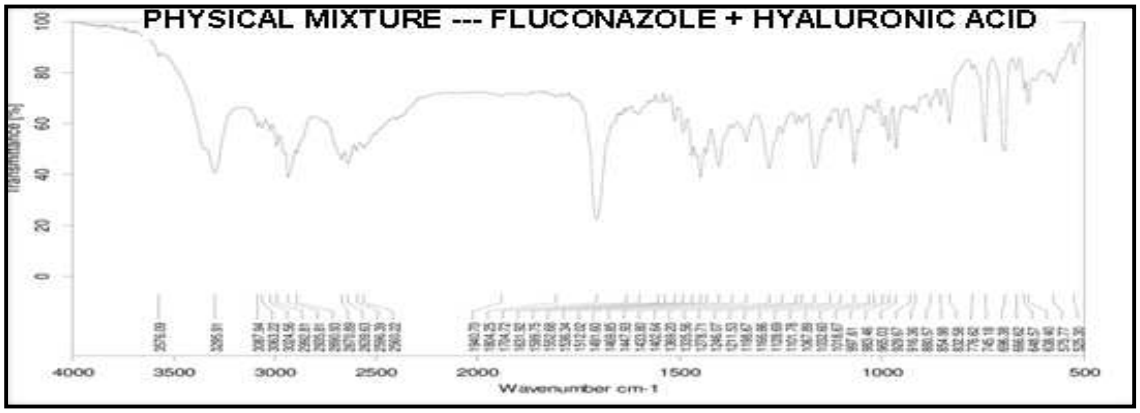

Figure No.4: FT-IR Spectra of Fluconazole + Hyaluronic acid

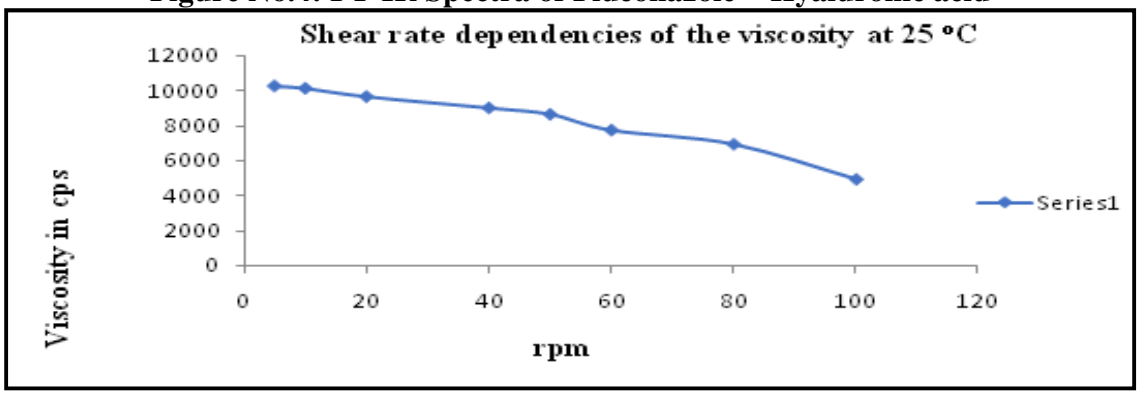

Figure No.5: Shear rate dependency of the viscosity at 25°C

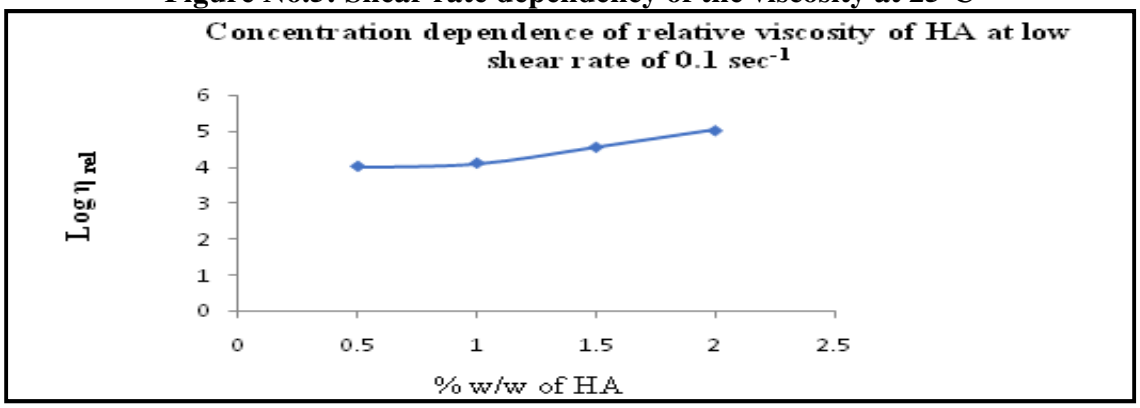

Figure No.6: Concentration dependence of the relative viscosity at a low shear rate for HA

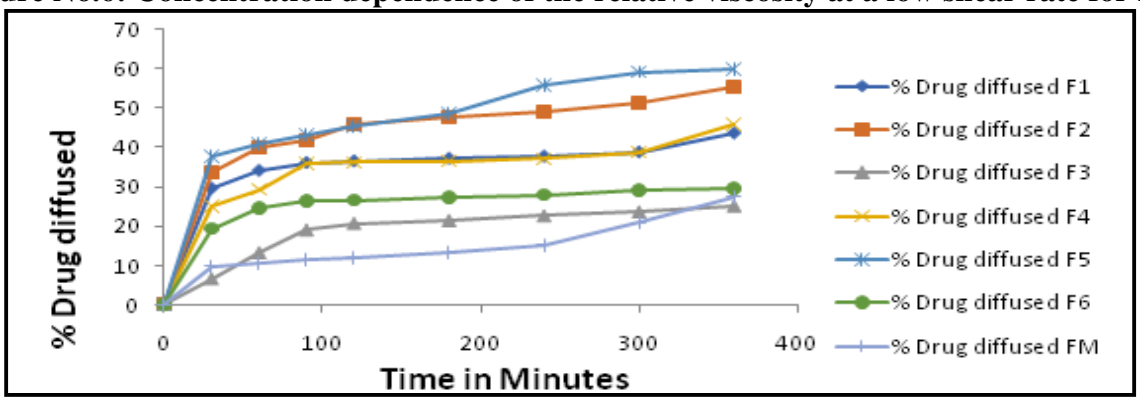

Figure No.7: Comparative drug diffusion plot of formulations F1-F6 and marketed

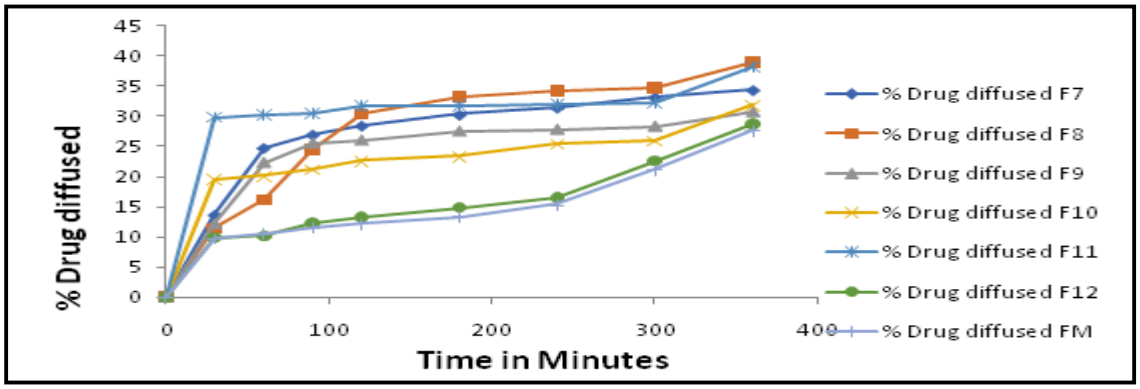

Figure No.8: Comparative drug diffusion plot of formulations F7-F12 and marketed

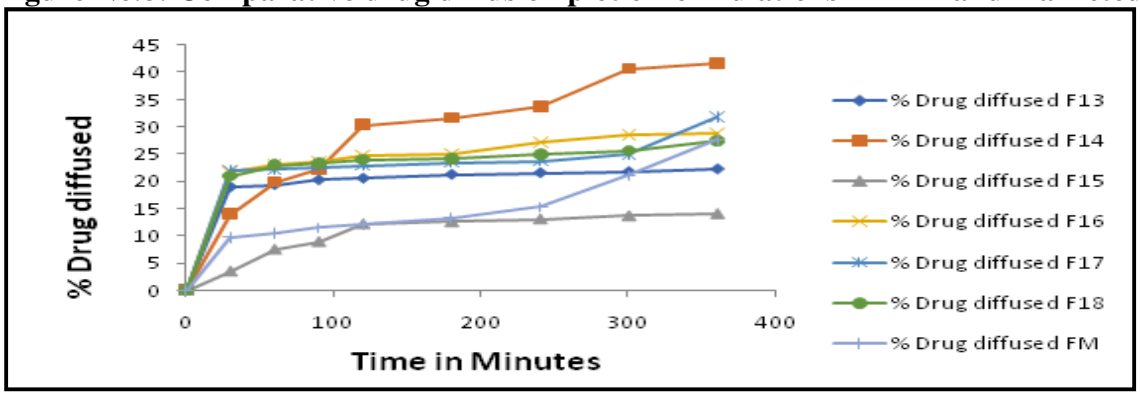

Figure No.9: Comparative drug diffusion plot of formulations F13-F18 and marketed

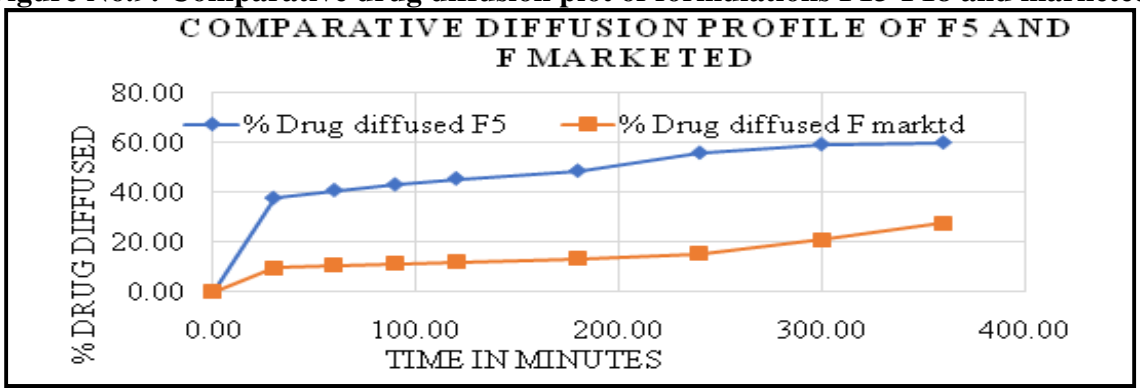

Figure No.10: Comparative drug release study between F5 and Marketed formulations

Figure No.11: Zone of inhibition of Placebo gel formulation

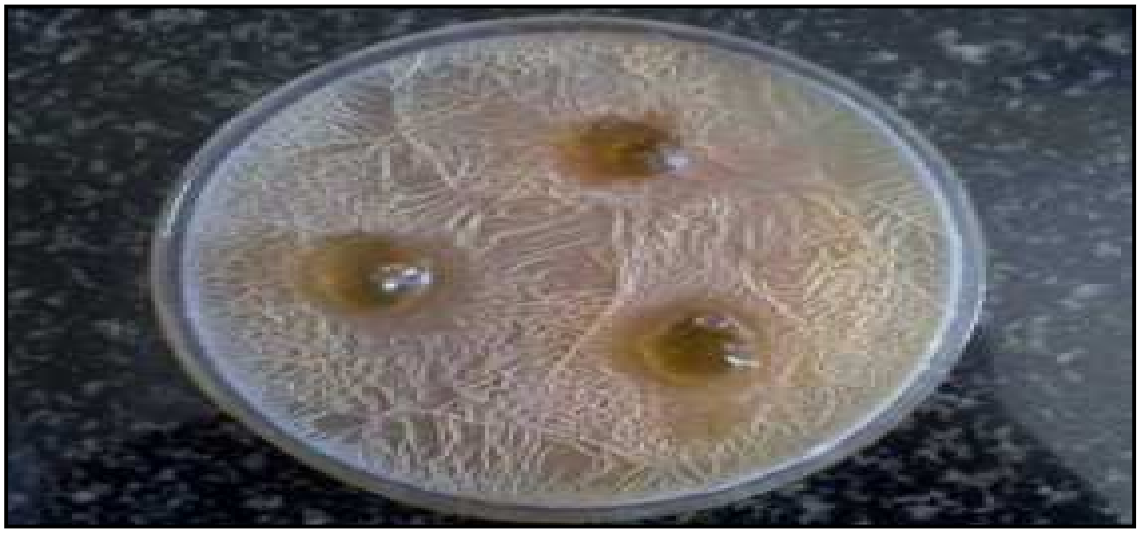

Figure No.12: Zone of inhibition of F5 hydrogel formulation

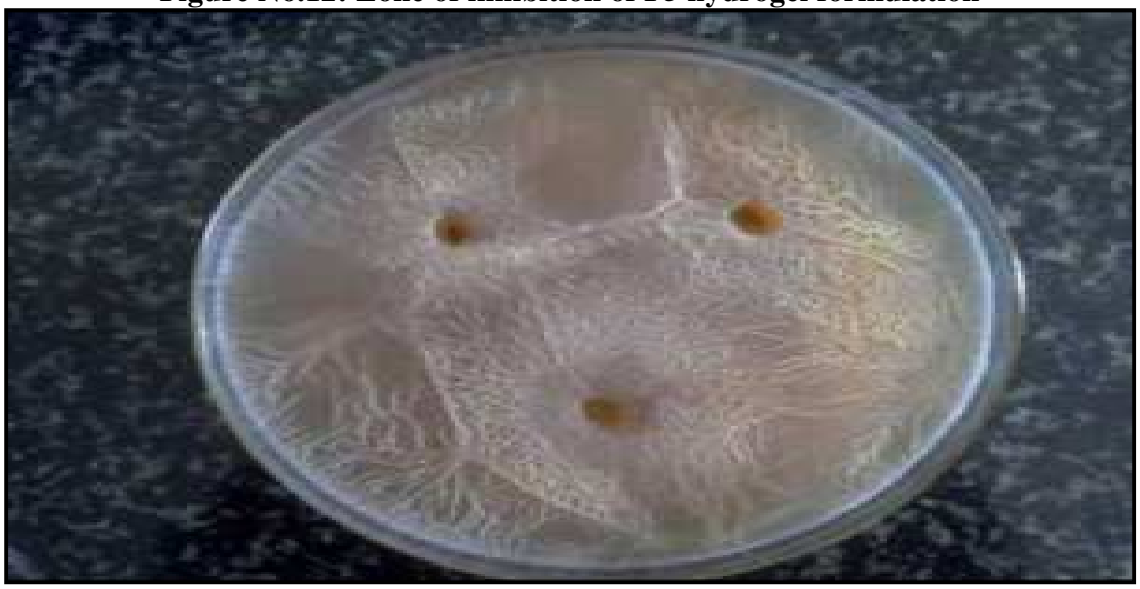

Figure No.13: Zone of inhibition of standard drug

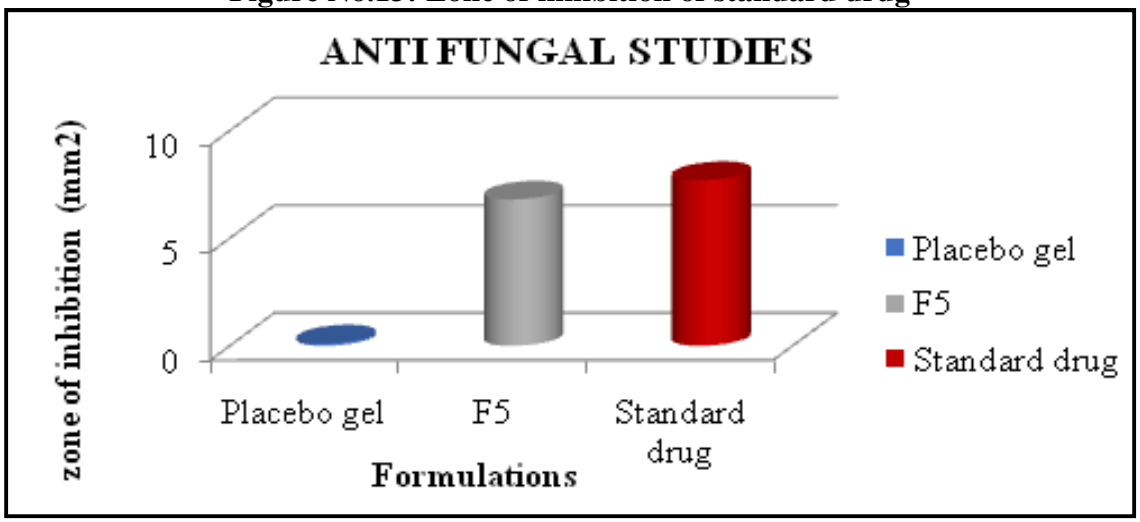

Figure No.14: Zone of inhibition of optimized hydrogel formulation

CONCLUSION

In the present investigation, studies were undertaken on the design of topical drug delivery system for the widely used drug Fluconazole. It is an antifungal drug for the treatment of wide variety of fungal infections. Hyaluronic acid hydrogels of fluconazole were prepared to improve patient compliance and improved duration of action. On the basis of the previous findings we can conclude that Fluconazole was successfully incorporated into the different topical hydrogel preparations. From among all the developed formulations F-5, showed good homogeneity, drug content uniformity, Spreadability, extrudability, viscosity, % drug diffused and antifungal activity. The Formulation F-5 with propylene glycol as permeation enhancer used in the study showed greater drug diffusion profile to that of the marketed product (Flucos). 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 observations are needed.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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