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FORMULATION AND EVALUATION OF TOPICAL SUSTAINED RELEASE FILM FORMING GEL OF FLUCONAZOLE

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ABSTRACT

The aim of the research work was to develop Sustained release topical film forming gel of Fluconazole. The gel containing fluconazole was prepared successfully using polymers hydroxypropylmethylcellulose K4M 2.0 % and Polyvinylpyrrolidone K30 2.0% optimized by 3^2 full factorial design. The optimized formulation showed drying time of 480 seconds, a release of 77%, tensile strength of 0.0614 and antifungal activity of 97.22%. The prepared formulation is effective against the superficial fungal infections and shows its efficacy for cutaneous as well as superficial fungal infections without drug's invasion into the systemic circulation.

KEYWORDS: Keywords: Film-forming solution, Film-forming system, controlled drug release.

INTRODUCTION

Topical route is one of the widely accepted route for drug delivery for superficial, cutaneous as well as systemic drug delivery as it offers advantages over the oral drug delivery. For avoidance of some disadvantages of the oral route like first pass metabolism, low pH, and enzyme hindrance makes topical drug delivery a better option. To improve therapeutic efficiency or pharmacokinetic profiles, topical drugs are delivered via lotion, creams, ointments, sprays, solutions, gels, and also with the help pre-formulated bioadhesive films known as patch.[1] These formulations mentioned above are having some disadvantages like stickiness, multiple dosing frequency, less bioavailability of the drug. However, though a patch is a better formulation with lesser disadvantages but it also has some disadvantages. Patch preparations are also often associated with hypersensitivity, irritation, and blistering.[2]

The recent innovation of the film forming system has come along with much reduced disadvantages in the topical drug delivery and has less chances for skin irritation hypersensitivity and provide controlled release of the drug. Film forming system can be delivered via film forming gels, solutions or spray.[3]

The film forming system is a novel approach for topical drug delivery where the formulation gives sustained release of the drug thus improving dosing frequency. The formulation has aesthetic look as well as it is transparent in nature. Thus there is increased patient compliance for the formulation due to above characteristics.[1]

Fluconazole is having moderate water solubility about 8mg/ml in water.[4] It is mainly fungistatic but also act as fungicidal in some organism in dose dependent manner. It is chemically 2-(2, 4-difluorophenyl)-1,3-bis(1,2,4-triazol-1-yl)propan-2-ol belonging to the azole category. It inhibits fungal growth by inhibiting fungal cytochrome P450 enzyme 14 demethylase of fungus.[5] There are different fluconazole formulations available in the market like gels, Tablets, creams, ointments etc.

The aim of this research is to develop a gel containing fluconazole which will form a film in situ upon skin on application within few minutes. It is a modified release formulation having more patient compliance due to lesser frequency of application and aesthetic look as it is transparent.[1]

MATERIALS AND METHODS

Materials

Fluconazole was received as a gift sample from. HPMC K4M and polyvinylpyrrolidone and the PEG 400 was received from the college. Other chemicals used were of laboratory grade.

Methods

Pre-formulation

Selection of solvents for fluconazole solubility

Solubility of fluconazole API was determined in different solvents which were to be used in the formulation. Solubility was checked in the solvent water, acetone, and ethanol individually. Also the solubility was checked in the combination of the solvents i.e. water, acetone and ethanol in the ratio 50:30:20 respectively. This ratio was determined by taking the solubility and drying time of the film in consideration. The same solvents system was

tested for the polymers solubility determination.

Selection of polymers

Various polymers were screened that can form gel as well as film. Various grades of Polaxomer, Hydroxypropylmethylcellulose, Polyvinylpyrrolidones and chitosan were analyzed for the ability to form gel as well as the film formation. The combinations were also tried for the same. The ability as well as quality of the gel and film formation were observed to select the best possible polymers. Polymers were also selected to achieve sustained release of the drug.

Fluconazole-excipient compatibility studies

Excipients and the fluconazole combinations (HPMC K4M, PVP K30, Ethanol and Acetone blend PEG 400) were kept in the oven at 40^0C in the dual combinations for 30 days.

FTIR analysis

The physicochemical compatibility must be established between fluconazole and the other main excipients like HPMC K4M and PVP K30 to produce a stable, efficacious, and safe product. The sample was taken of fluconazole, pure excipients, and physical mixture of formulation in equal proportion were mixed together and kept at 40^0C. Initial analysis was done by FTIR and then after 30 days, the drug excipient combinations were observed physically as well as in IR for the compatibility studies. The scanning range was 450–4000 cm^{-1} and the resolution was 1 cm^{-1}.[6] The FTIR graphs are shown in the Fig 1.

Preparation of Gel

Accurately weighed quantity of hydroxypropylmethylcellulose K4M was taken in the 50 ml of water and allowed to swell for 2 hrs. In another beaker weighed quantity of polyvinyl pyrrolidone K30 was taken in solvents ethanol and acetone in the ratio of 20:30 and mixed well using a magnetic stirrer at optimum speed. The drug was added to this polymeric solution. Later the solution containing polyvinyl pyrrolidone and the drug was added slowly into the solution containing hydroxypropylmethyl cellulose with continuous stirring. The formed solution was enclosed in a sealed container kept on the magnetic stirrer and stirred for 4 hrs.[7-10]

Factorial Design

For optimizing the formulated product, a 3^2 full factorial design was used. According to the

literature review, the concentrations of HPMC K4M (X1) and PVP K30 (X2) were chosen as independent variables, while the Drying time (sec) (Y1) and the drug release (Y2) were chosen as dependent variables. The response to composition is linked to a mathematical model. There were variables for each factor, as well as qualitative levels for each excipient. Design-Expert software was used to optimize the formulation.[11] 9 batches were prepared for the optimization as given in the Table 2. and the formulation batches were evaluated for the drying time, drug release, tensile strength and aesthetic nature.

Formulation evaluations

Drying time

For the drying time measurement the formulations were applied on the different glass slides. The applied formulations were checked using cotton frequently after it seemed to be dried. A small cotton piece was swapped over the formulation applying very small pressure with delicate hand and sticking was observed to check drying. The time at which no cotton threads got stuck was noted as drying time.[8]

***In vitro* Drug release Study**

In a Franz diffusion cell, a nylon membrane with a pore size of 0.22 µm was used. The available surface area of the membrane for drug transport was 2.2 cm^2. The donor and receptor compartments were filled with two milliliters of the drug formulation and 13 ml of solution (pH 7.4, 100 rpm) containing 0.9 percent w/v sodium chloride and 1 percent w/v sodium lauryl sulphate, respectively. Using a hot-water jacket (32°C), the temperature of media in the receptor compartment was maintained at 32°C throughout the experiment. Fluconazole was measured spectrophotometrically at 261 nm in aliquots of 1.0 ml samples taken from the receptor compartment at intervals of 2 hrs. After each withdrawal, an equal amount of fresh dissolution medium was replaced to maintain the sink condition.[4],[12]

Tensile strength

Tensile strength was measured using ‘Ubeque Tensile Tester’. All the nine formulations were evaluated for the tensile strength using the tensiometer. A good tensile strength shows the good mechanical strength of the film.[13,14]

Aesthetic nature

The film formed was evaluated for its aesthetic looks visually. The formed films of different polymeric gels were graded as clear, slightly opaque.

Optimization and validation of model

The data of *in vitro* release and drying time was fed into the design expert software 12.0, which created the equations. The numerical optimization was carried out with the help of the desirability function, and the projected formula was examined to see if the outcome matched DOE's optimized release data.

Evaluations for optimized formulation

***Ex vivo* skin permeation Study**

In vitro drug absorption into the skin was estimated by the *in vitro* skin permeation test. Rat skin was used as the diffusion membrane to simulate human skin. The skin was wiped with the cotton soaked in isopropanol to remove any adhering fat and the skin. The membrane of 2 cm^2 was mounted on the Franz diffusion cell between the donor and the recipient chamber. 2 ml of the gel was applied onto the skin from the donor compartment. The system was kept at constant temperature of 32±1°C. After 8 hrs. the skin was removed and the residue was washed with 10 ml methanol, filtered and was analysed under UV to get the amount of drug that remained on the skin. The solvent in the recipient chamber was also analysed under UV at 261 nm to get the drug amount that passed through the skin. So ultimately the drug that has absorbed in the skin was also estimated.[15,16,17]

Viscosity

Brookfield viscometer (digital viscometer model DV-II+, Stoughton, MA, USA) was used to measure the viscosity of the gel at 32°C. The C93 spindle was rotated at 1 revolution per minute.[9]

Texture analysis

Texture analysis of the optimized formulation was determined by the hardness as well as adhesiveness of the gel. An optimum values of the same shows the better spreadabilty of the gel on skin. For the texture analysis the Brookfield Texture Analyser was used.[16]

Drug content

Drug content was estimated using methanol as solvent. Accurately weighed 10 mg of the gel was taken and solubilized in the 10 ml methanol. 1 ml of aliquot was taken and again diluted in 10 ml methanol. The solution was then analyzed in the UV at λ max 261 nm for the absorbance.[9]

Water vapor permeability test

The water vapor permeability (WVP) was investigated using a modified British Pharmacopoeia method. As previously stated, films were created using a solvent evaporation technique. A scalpel was used to cut circular samples with a diameter of 2.0 cm from dry film sheets. For the sample preparation, 10 ml glass vials with a 1.2 cm diameter opening (A = 1.13 cm^2) were filled with approximately 8 g of distilled water, covered with circular film samples. The top of the vial cap was opened to begin the experiment, and the weight of the vial was determined using an analytical scale. The vials (three per formulation) were then placed in a desiccator with a desiccant to create a low relative humidity environment (approximately 0 percent). They were weighed after 72 hours of being kept at a specific temperature (37°C). Using the following formula, the WVP was calculated from the weight loss of the vials W (g) as the amount of water that had permeated through the film in relation to the surface area (A cm^2) and time (t, 24 hours) [18]. According to the British Pharmacopoeia a film can be considered permeable to water vapor when the WVP exceeds 0.05 g cm^{-2} $24h^{-1}$.

Formula used:

$$WVP = W/ (A*t) (g\ cm\text{-}2\ 24\ hrs\text{-}1)$$

Antifungal efficacy study

Antifungal drug efficacy of the optimized formulation was performed using cup plate method. The fungi Candida albicans (NCIM No. 3674) was received from the National Collection of Industrial Microorganism, Pune. The fungal culture was revived using streak plate technique. For the revive process, the fungi was streaked on the Sabourad Dextrose Agar medium containing 2% of agar and to grow at 30°C in the incubator. The grown culture was was then inoculated in the sterilized Soybean casein broth and kept in the mechanical shaker at 30°C for a day. The grown culture was then poured in the five sterilized petri plates in aseptic condition and mixed with the 20 ml sterilized SDA media in each 4 petri plates. After solidification of the media, each petri plates was bored using cup borer to form the wells. 2 wells were bored in each petri plates. Formulations were added into the well as shown in Table 3. Zone of inhibition was recorded after 24 hrs.[19]

***In vivo* skin irritation study**

The skin irritation study on rats was approved by the Institutional Animal Ethics Committee with approval no CPCSEA/IAEC/PT-18/02-2K21. 9 rats were taken and divided into three

groups, each group containing 3 rats. Hairs of the rats were removed using the hair removing cream and the area was washed with clean water. One group was treated with the optimized formulation. Second group was treated with the standard irritant 0.8% of formalin. The group 3 was considered as control. The area of application was washed every time after removal of the film. The same procedure was continued for 7 days. The test area of the skin was observed for every 24 hrs. for a week to check erythema and edema.[20] (Table 3)

RESULTS AND DISCUSSION

Selection of solvents for fluconazole solubility

Fluconazole was found to be slightly soluble in water i.e. 1.2 mg/ml. Solubility of fluconazole in the ethanol was found to be 22 mg/ml and solubility in acetone was found to be less than 20 mg/ml. Thus the fluconazole is highly soluble in both ethanol and acetone. Fluconazole solubility in the blend of water, ethanol and acetone in the 50:30:20 ratio was found to be more than 20 mg/ml. Due to adequate solubility of the drug and the presence of both the volatile and non-volatile solvents, the triple blend of solvents was selected. (Table 4)

Selection of the polymers

A preliminary study was done using different film-forming and gel-forming agents taking the solvents decided for drug solublization into consideration. HPMC K4M and PVP K30 were selected as they have ability to achieve the aim. Both the polymers are biocompatible, water soluble along with pursuance of significant viscosity after gel formation. HPMC K4M is a gel forming polymer and gives sustained release by drug diffusion by entrapped drug into its polymeric matrix. Also PVP K30 is itself a sorbent. Water soluble monomers of PVP K30 appears to be particularly promising with significant possibilities of hydrogel polymeric matrix formation.[21] Both the polymers are also able to form a gel in the selected solvent blend.

Drug excipients compatibility studies

Physical observation

All the combination of the fluconazole and the excipients were observed visually and the results is shown in the Table no. 2 in tabular form. There was no change in the physical appearance of all the combinations after 30 days. So we can say that there was no physical as well as chemical interaction between the drug and excipients and the excipients is compatible with the drug.

FTIR analysis

The result of FTIR analysis for the drug excipient compatibility studies is shown in the Fig 1. The peaks obtained of pure fluconazole is same as the peaks obtained at from the fluconazole and excipients (HPMC K4M and PVP K30) in combination. The OH stretch of the pure fluconazole i.e. at 3131 cm^{-1} has no change in the fluconazole and the HPMC and PVP combination. Also the C=N stretch was found at 1620 cm^{-1} in fluconazole in combination with the same excipients which indicates no change in the C=N stretch of the pure fluconazole. This confirms that there is no interaction between the drug and polymers and polymers are not making change in the drug's chemical structure and functional group necessary for the drug's activity (Table 5).

Drying time

Drying time of the A1 was observed to be the minimum and was maximum for A9. The drying time was increased from A1 to A9 consecutively (Fig 2). Addition of HPMC K4M and PVP K30 increases drying time. Due to its hydrophilic nature of both the polymers, they allows the solvent to diffuse into the polymer. As water penetrates into the polymer, it forms a reservoir of water in the matrix of polymeric chain and get swollen.[22] As the concentration of polymer increases the water reservoir in the matrix also increases and unable to squeeze out easily results in increased drying time (Table 6).

***In vitro* Drug release Study**

Drug release from the formulation was highest in the A1 batch which has the lowest amount of polymers. While the lowest release was found to be from A9 batch which has the highest polymers concentration. Drug release pattern from the gel was observed to be decreasing from A1 to A9 (Table 7). The HPMC and PVP are acting as release retardants. These are hydrophilic polymers that form viscous gel. The drug is dispersed in the gel matrix. As the gel forms the film, the drug gets entrapped in the matrix of the polymers and diffuse out slowly from the film, as HPMC K4M makes a reservoir of drug into the polymeric chains and PVP K30 keeps adsorbed drug on the pyrrolidone ring of macromolecules resulting in the prolonged release of the drug.[23] Concentration of both the polymers shows the indirect relationship with the drug release. As the polymer concentration increases the ability of holding the drug into the matrix increases leading to increase in retardation of the drug. (Fig 3).

Tensile strength

Tensile strength of the film showed an increasing order pattern from A1 to A9. It was observed that the formulation A1 is least tensile while the formulation A9 is the most tensile. Tensile strength is showing direct relationship with the polymers concentration. Increase in the concentration of the polymers causes more swelling of the polymer leading to form a more viscous gel ultimately increasing the tensile strength of the formed film [24]. (Table 8) (Fig 4).

Aesthetic nature

The A1 formulation has most cosmetic attractiveness as it is forms the clearest and a very thin film which was not catchy to eyes on the skin easily. There was not that much difference observed in comparison to the last three films in the successive two formulations (i.e. A2 to A4) but the films of the formulations A5 and A6 observed to be slight opaque. Films formed from the formulations A7 to A9 were found to be slightly more opaque than the A5 and A6 with increased film thickness which could be easily catch the eyes attention (Table 9). Gel becomes more viscous with increasing concentration of the polymers so opacity of the film the increases with the increasing in the polymer concentration (Fig 5).

Analysis of optimized data

The experimental design was evaluated and the analysis of experimental results were done by stat-Ease design expert. The ANOVA, P-value, and Model F value for percent drug release and drying time were obtained. (Table 10)

The drying time between experimental batches varied between 480-810 seconds. The % drug release varied between 35-77 %. The response surface graph shows direct dependence of drying time on PVP K30 and HPMC K4M whereas showing indirect relation with drug release on increasing polymers' concentration. (Figure 6 and 7). Thus the formulation batch giving optimum % drug release and drying time was chosen as optimized batch based on desirability function. The optimized formula was subjected to verification and no significant difference between the theoretical and actual values (Table 11).

Drug release= +64.33-17.17 *A -3.67 *B -0.75 *A*B -6.50 *A2 -1.00 * B2

Drying time= +639.56 +124.33 *A + 40.17*B +2.75*A*B +0.67*A2 +2.17*B2

***Ex vivo* permeation study**

Ex vivo permeation study is important to check whether the formulation prepared is

permeating at desired site or not. As the formulation is for superficial as well as the cutaneous infections of fungus, the drug should permeate into the skin layers also should be available at the skin surface for longer duration of time. After 8 hrs. The drug permeated through the skin into the receptor chamber and was found to be 2.16 %. The drug that remained over the surface skin was found to be 40.02% and the drug estimated for the skin retention was 55.64%. Due to hydrophilic nature of HPMC and the drug fluconazole, only 2% of the drug entered the receptor chamber through the skin. Since ethanol and acetone together act as penetration enhancers the drug penetrated into the skin layers and about 55.64% was retained. Also 40.02% of the drug remained over the surface of the skin. Thus the formulation is able to inhibit the fungal growth on the surface as well as in the cutaneous layer of the skin. Very less permeability of the drug through the skin into the receptor compartment shows lesser availability of the drug in the systemic circulation thus having no systemic effects. (Table 12)

Viscosity

Viscosity of the optimized formulation was found to be 5030 cP at 100 RPM and 50.3 % torque. The viscosity of the formulation is adequate that the gel is retaining at infected site and also easy for the application. HPMC concentration is the factor which is responsible for the increasing and decreasing of the viscosity.[24] The F1 formulation is having the lowest amount of HPMC probably be having the best spreadability among all the others with greater amount of HPMC.

Texture analysis

Hardness of the gel was found to be 39.30 g and the adhesiveness of the gel was found to be 0.24 mJ. It shows that the formulation is having adequate hardness. The gel is easily applicable and able to retain at the infected site thus there is no loss of the drug.

Drug content

Drug content test of the optimized formulation was observed to be 98.66 %

Water vapor permeability test

The weight of water remaining in the glass vial was 6.34 g out of 8 ml of water in the vial. The water vapor permeability of the optimized formulation was found to be 0.0612.This shows that the film formed in permeable to water. Adequate water permeability is needed to pass the water from the skin to the environment. Also this helps in keeping the film moist throughout its availability on the skin.

Antifungal efficacy study

The T1 formulation showed the highest zone of inhibition which is 97.22 % of the standard zone of inhibition. T2 containing placebo formulation showed the least zone of inhibition which is 20 % of the standard ZOI. T3 containing only solvent (ethanol and acetone blend) showed the third highest ZOI but closer to the placebo ZOI which is 24% of the standard ZOI. T4 containing the fluconazole along with the ethanol and acetone blend showed the ZOI closer to the T1 which is 94.44%. The observations are indicating that the formulation is having the good antifungal efficacy. Presence of an ethanol is also helpful in the inhibiting the fungal growth.[25] (Table 13) (Fig 8 and 9).

***In vivo* skin irritation study**

The formulation showed no irritancy to skin of the rats upto day 7. But the rats treated with the skin irritant showed mild irritation after day 2. Negative controls showed no skin irritation throughout 7 days. The results shows that the drug and the excipients are showing no adverse effects on the skin are biocompatible and so the prepared formulation is suitable to use on the human skin as it shows no irritancy to the rat skin. (Table 14) (Fig 10).

Table 01: Optimization Batches.

Ingredients (% w/w)	BATCH CODE								
	A1	A2	A3	A4	A5	A6	A7	A8	A9
Fluconazole	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
HMPC K4M	2.0	2.0	2.0	3.0	3.0	3.0	4.0	4.0	4.0
PVP K30	2.0	3.0	4.0	2.0	3.0	4.0	2.0	3.0	4.0
PEG 400	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Water	50	50	50	50	50	50	50	50	50
Ethanol : Acetone (80:20)	50	50	50	50	50	50	50	50	50

Table 02: Antifungal Efficacy Testing.

	Plate No.	T1	T2	T3	T4
Testings	1	Optimized Formulation	Placebo	Ethanol: Acetone (80:20)	Fluconazole dissolved in Ethanol and Acetone blend
	2	Optimized Formulation	Placebo	Ethanol: Acetone (80:20)	Fluconazole dissolved in Ethanol and Acetone blend

Table 03: *In Vivo* Skin Irritation Study Draize Scoring.

Scoring	Erythema	Edema
0	No erythema	No edema
1	Very slight erythema	Very slight edema
2	Well- defined erythema	Slight edema
3	Moderate to Severe erythema	Moderate edema
4	Severe erythema	Severe Edema

Table 04: Fluconazole Solubility In Different Solvents.

Sr. No	Solvents	Solubility
1	Water	1.2 mg/ml
2	Ethanol	22 mg/ml
3	Acetone	>20 mg/ml
4	Water: Ethanol: Acetone (50:30:20)	Soluble

Table 05: Excipients and The Fluconazole Compatibility Results.

Sr. no	Fluconazole with	IR observation	Physical appearance
1	HPMC	No peaks shifting	No change
2	PVP	No peaks shifting	No change
3	PEG 400	-	No change
4	Ethanol and acetone blend	-	No change

Table 06: Drying Time Result.

Sr. no	Batch Code	Drying Time (Secs)
1	A1	480
2	A2	519
3	A3	553
4	A4	600
5	A5	639
6	A6	684
7	A7	726
8	A8	762
9	A9	810

Table 07: *In Vitro* Drug Release Study.

Sr. no	Formulation No.	Drug Release in 8 hrs (%)
1	A1	77
2	A2	76
3	A3	70
4	A4	66
5	A5	64
6	A6	61
7	A7	45
8	A8	40
9	A9	35

Table 08: Tensile Strength.

Sr. no	Formulation No.	Tensile strength
1	A1	0.0614 ± 0.0003
2	A2	0.0712 ± 0.0002
3	A3	0.0709 ± 0.0001
4	A4	0.0653 ± 0.017
5	A5	0.0986 ± 0.0002
6	A6	0.109 ± 0.001
7	A7	0.1263 ± 0.0015
8	A8	0.1526 ± 0.0030
9	A9	0.1846 ± 0.0030

Table 09: Aesthetic Nature.

Sr. no	Formulation No.	Cosmetic Attractiveness
1	A1	Clear, thin
2	A2	Clear, thin
3	A3	Clear, thin
4	A4	Clear, thin
5	A5	Slight opaque, slight thick
6	A6	Slight opaque, slight thick
7	A7	Slight opaque, thick
8	A8	Opaque, thick
9	A9	Opaque, thick

Table 10: Anova Output For Optimization Of Film Forming Gel.

Sr no.	Outcomes	Drying Time	% Drug Release
1	Models	Quadratic	Quadratic
2	R2 Value	0.9997	0.9967
3	F – Value	1763.68	181.81
4	P – Value	0.4350	0.4049
5	Adequate Precision	118.204	34.89

Table 11: Validation For Optimized Batch.

Formulation Code	Composition of optimized formulation		Predicted value	Actual value
	HPMC K4M	PVP K30		
Optimized batch	2	2	76.91% (drug release)	74.22% (drug release)
			480.63 seconds (drying time)	495 seconds (drying time)

Table 12: *Ex Vivo* Permeation Study.

Time (hrs.)	% cumulative drug permeated in the receptor chamber	% Drug remaining on the skin	% Drug estimated for skin retention
1	1.14	-	-
2	2.62	-	-
4	4.4	-	-
6	6.65	-	-
8	8.87	40.02	49.16

Table 13: Antifungal Efficacy Study Result.

Sr. no	Formulation No.	Zone of Inhibition (mm)	% Zone of inhibition
1	Standard	18	100 %
2	T1	17.5	97.22 %
3	T2	3.6	20.0 %
4	T3	4.3	24.0 %
5	T4	17.0	94.44 %

Table 14: *In Vivo* Skin Irritation Study; Draize Score Results.

		Score						
	Days	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Groups	Test	0	0	0	0	0	0	0
	Negative Control	0	0	0	0	0	0	0
	Positive Control	0	0	1	1	2	2	2

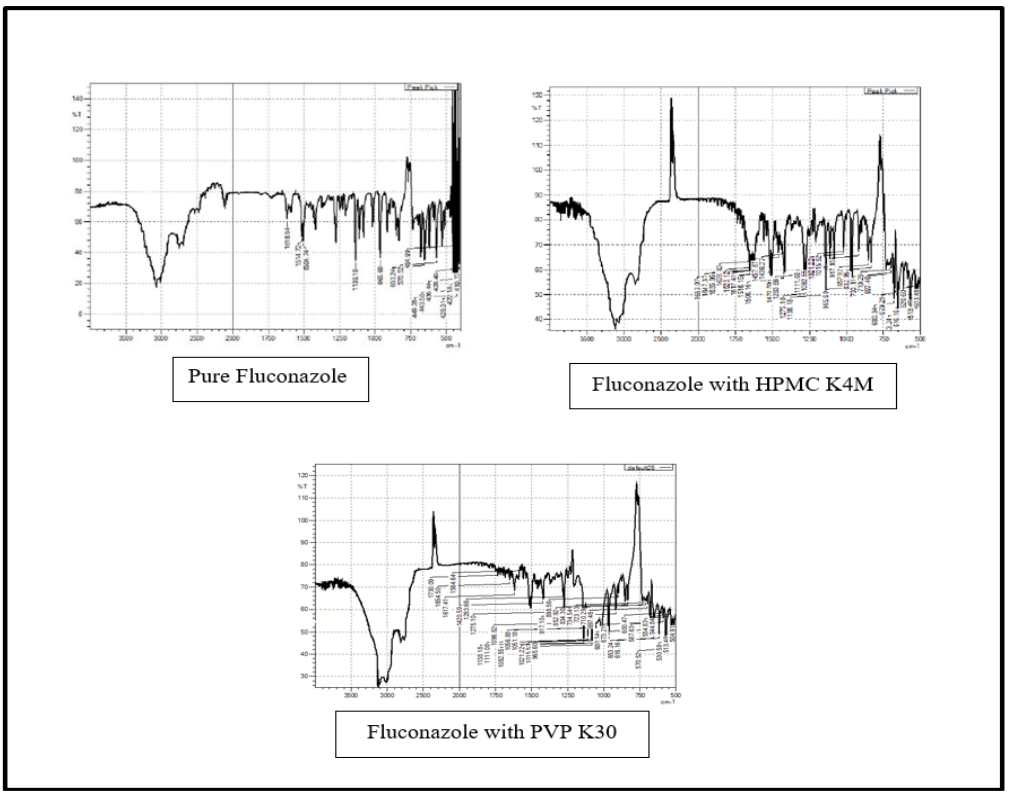

Fig 1: Fluconazole – Excipients Compatibility I.

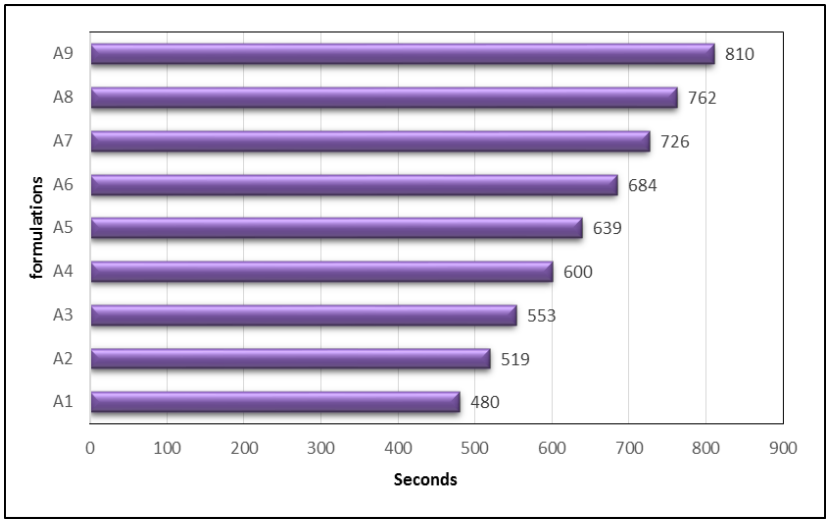

Fig. 2: Drying time.

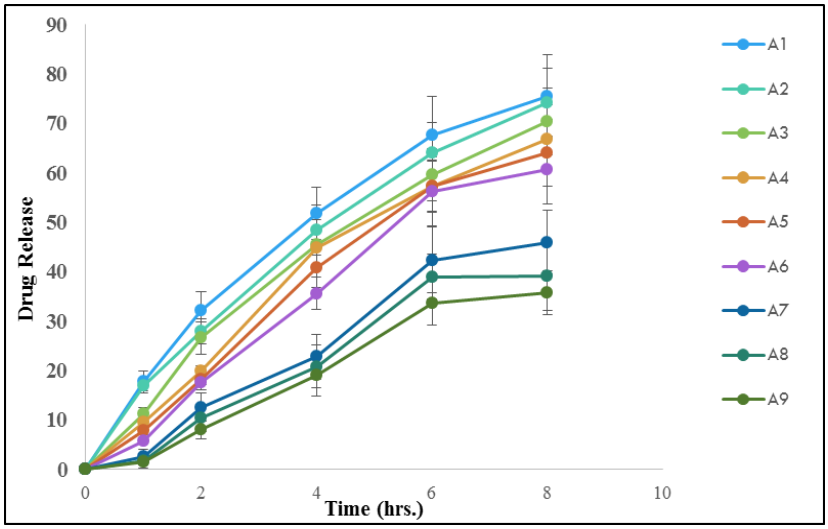

Fig. 3: Cumulative drug release pattern in 8 hrs.

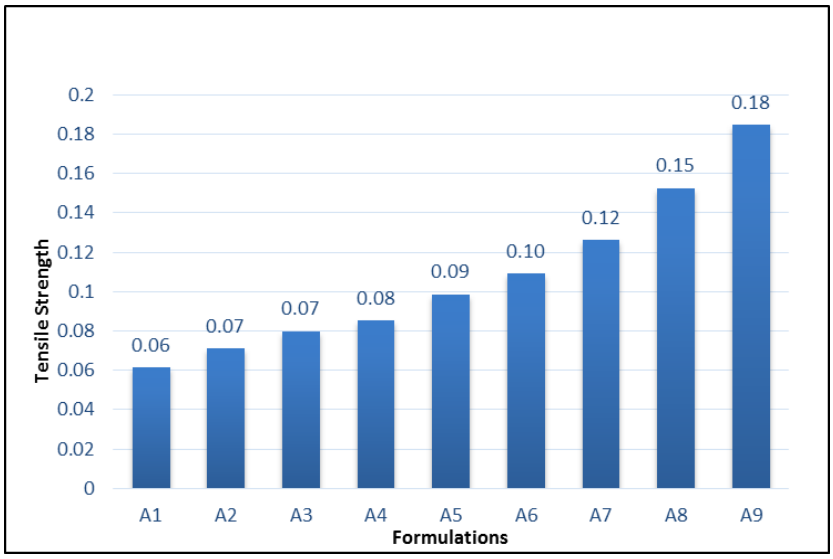

Fig. 4: Tensile strength of the films.

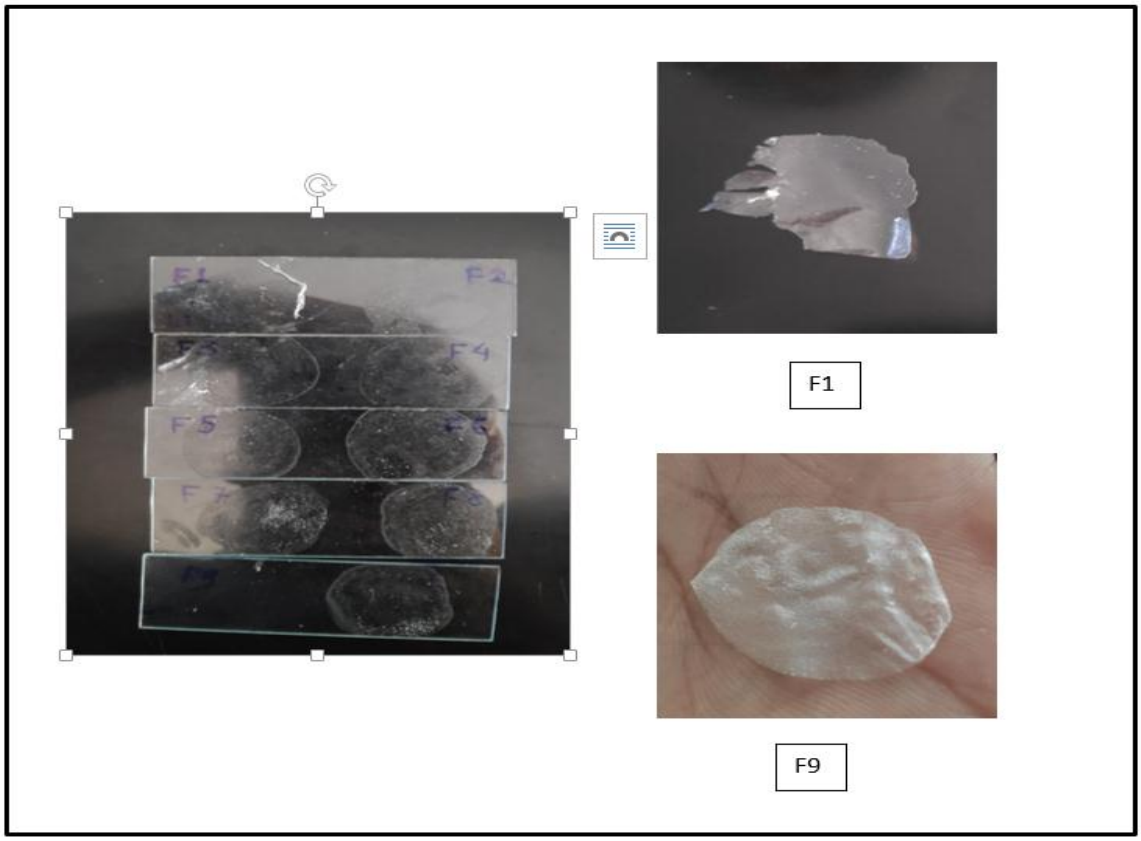

Fig. 5: Aesthetic nature.

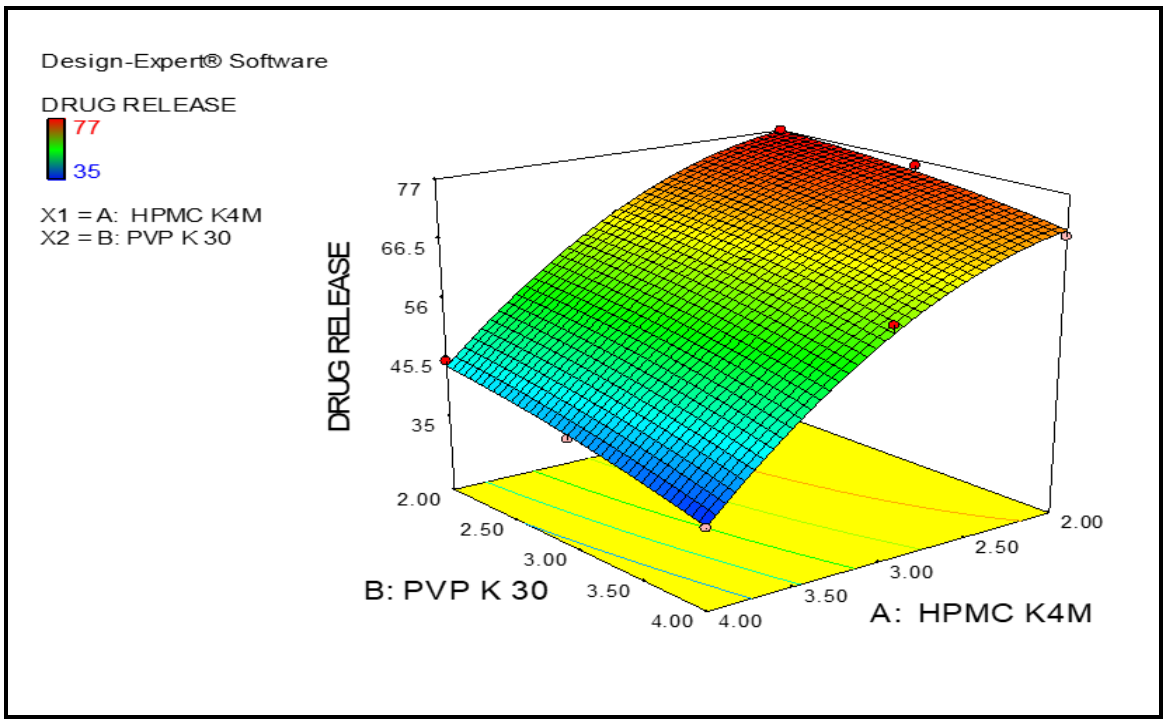

Fig. 6: Response surface plot showing the effect of PVP K30 and HPMC K4M on drug release.

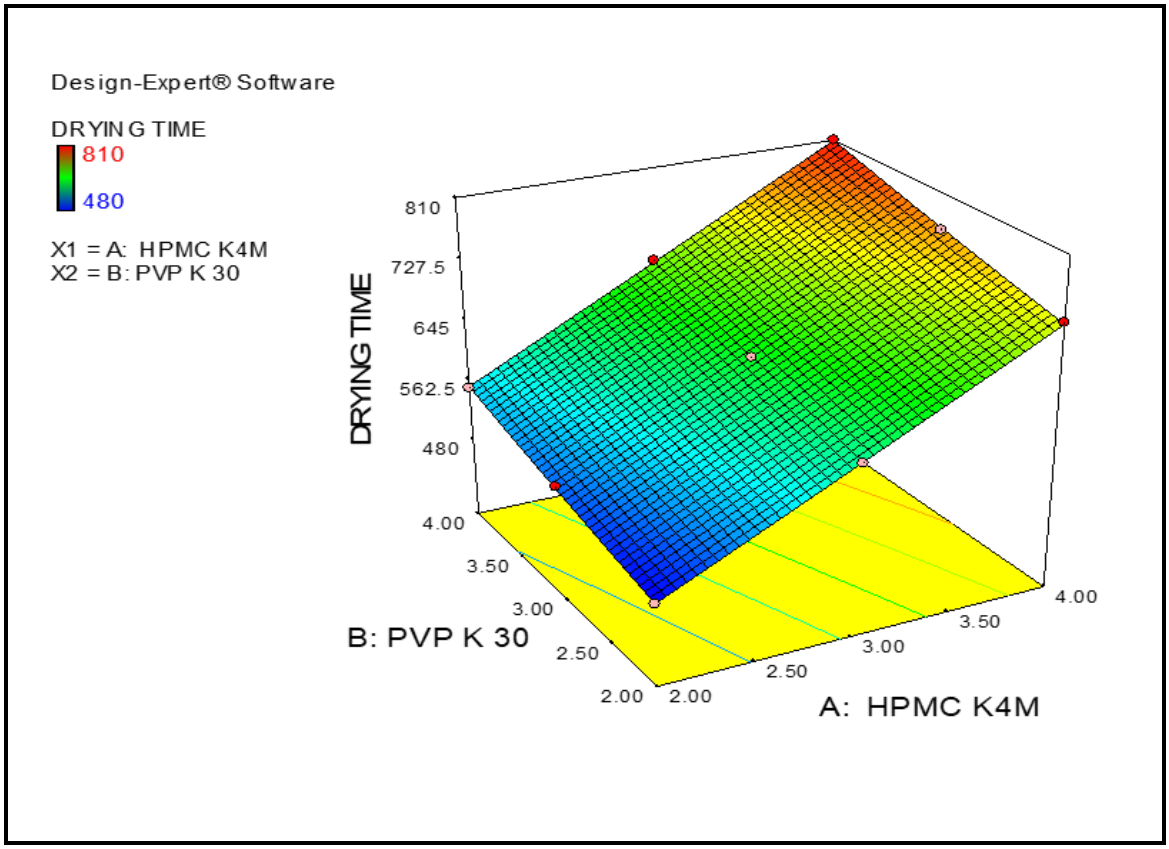

Fig. 7: Response surface plot showing the effect of PVP K30 and HPMC K4M drying time.

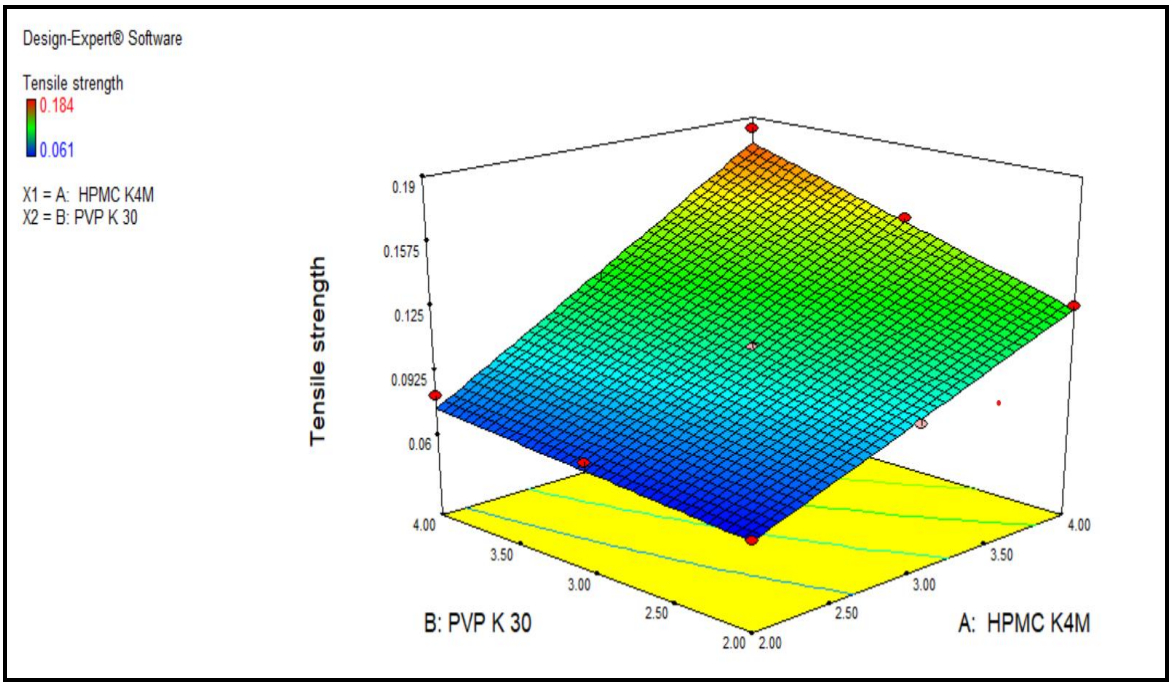

Fig. 8: Response surface plot showing the effect of PVP K30 and HPMC K4M on tensile strength.

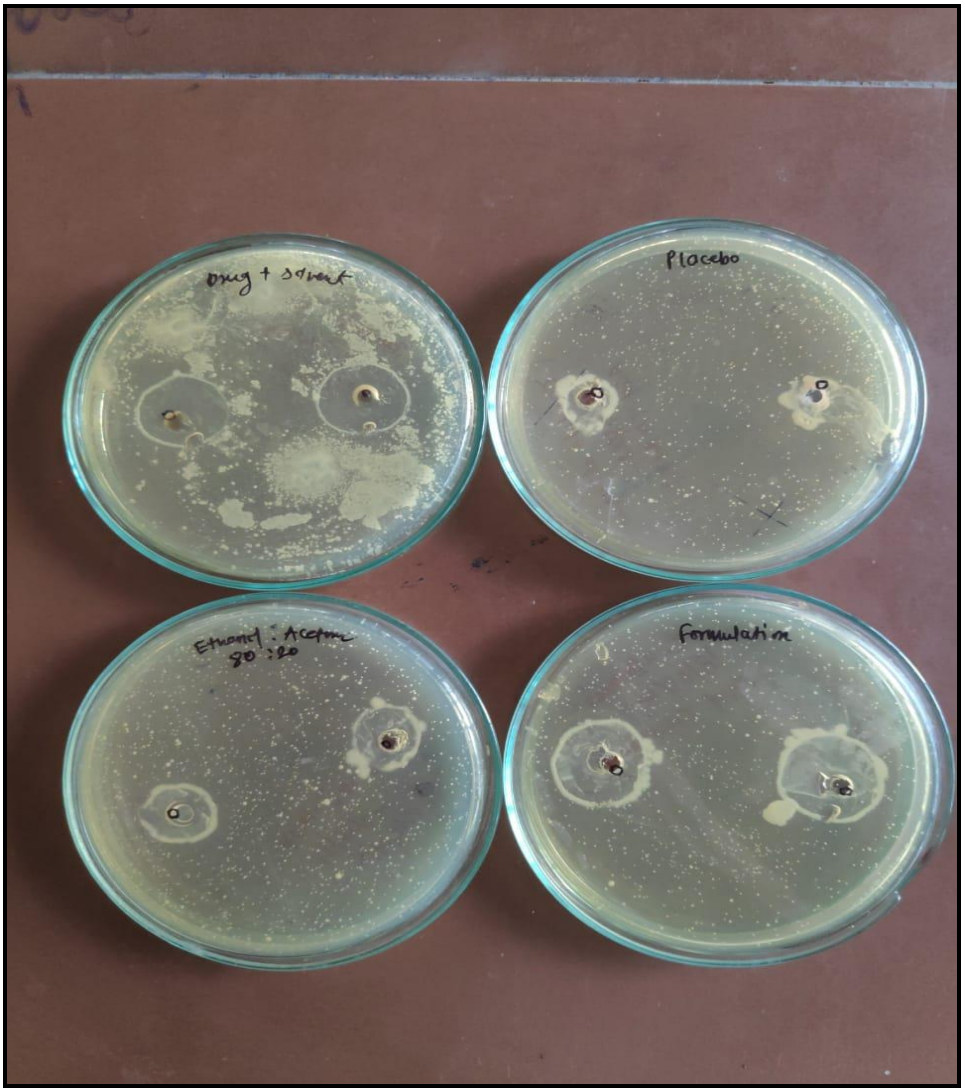

Fig. 9: Antifungal efficacy (Zone of inhibition).

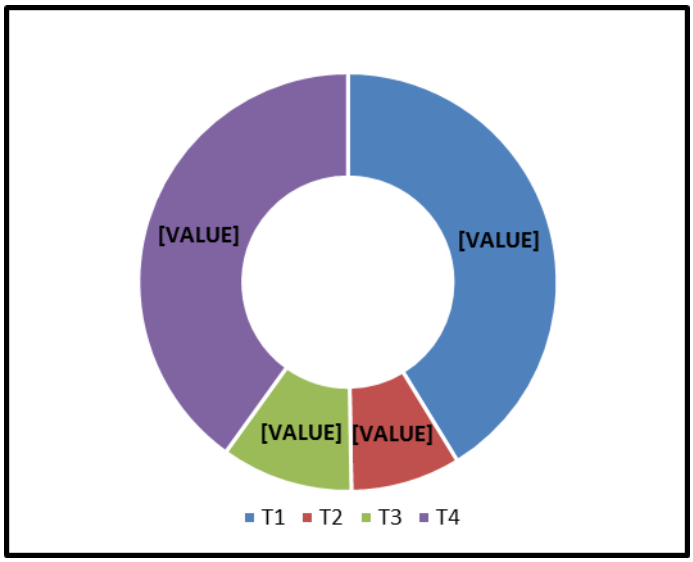

Fig. 10: Antifungal efficacy (Graphical representation).

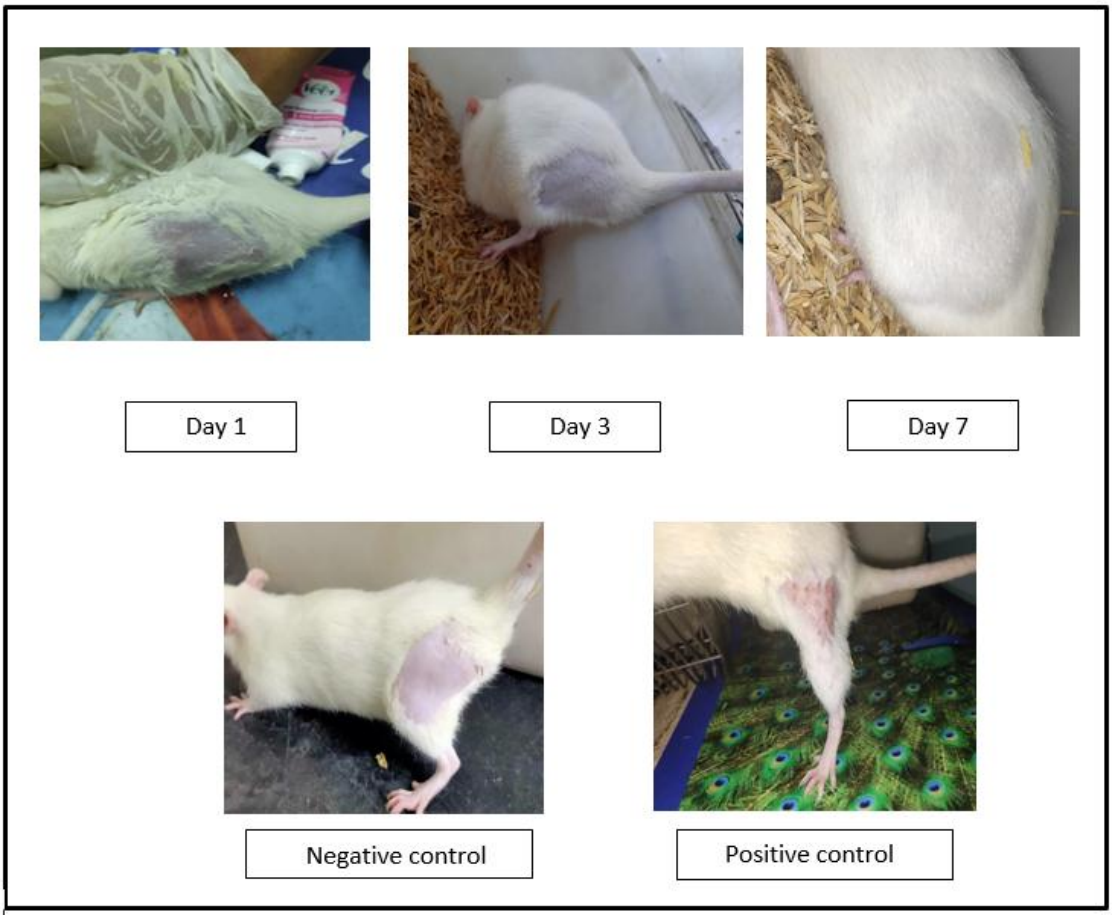

Fig 11: *In vivo* skin irritation study.

CONCLUSION

Patient compliance and drug targeting at the desired concentration are still concerns for effective treatments, even after the many available approaches for topical drug delivery. The film-forming system is a novel approach that has great potential for surpassing the disadvantages of the other dosage forms (hydrogels and films) along with controlled drug-releasing properties. A stable topical Sustained release film forming gel of fluconazole was prepared successfully using polymers hydroxypropylmethylcellulose K4M and Polyvinylpyrrolidone K30 optimized by 3^2 full factorial design. Thus desirable goal could be achieved of sustained release of the drug and making it advantageous over conventional gel by reducing dosing frequency. Antifungal activity along with the dermal safety were also proven and the prepared formulation product is effective against the superficial fungal infections and safe to use. The penetration of the drug into the systemic circulation is much minimum and the drug deposition into the skin is optimum. Thus the formulation shows its efficacy for only cutaneous as well as superficial fungal infections without drug's invasion into the systemic circulation.

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