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Research Article

A study on antifungal hydrogel for topical drug delivery of clotrimazole

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ABSTRACT

Hydrogels have the advantage over the conventional dosage forms for the topical delivery of antifungal drugs owing to its better pharmaceutical properties and penetration of drug to deeper tissues of skin. The present study was conducted to develop an antifungal hydrogel of clotrimazole. The results from characterization of developed hydrogels suggests that this formulation can cave better patient compliance and good drug release.

Key words: Hydrogel, antifungal, topical, clotrimazole.

1. Introduction

Topical delivery of drugs is recognized as an effective means of therapy for local dermatological conditions. Drugs are ad ministered topically for their action at the site of application or for systemic effects[1]. Among the various options available for topical drug delivery hydrogels can be a better delivery system due its better pharmaceutical properties and drug release profile. Hydrogels are polymeric network that absorb large quantities of water while remaining insoluble in aqueous solutions due to chemical or physical cross linking of individual polymer chains. The water content in hydrogels the hydrogels affect different properties like permeability, mechanical, properties, surface properties and biocompatibility. Hydrogels are water swollen three dimensional structures composed of primarily hydrophilic polymers. These are crosslinked macromolecular network that are insoluble but able to swell rapidly in water or biological fluid[2].

Fungal infections of the skin are one of the often-faced dermatological diseases worldwide. The efficiency of topical antifungal treatment depends on the drug penetration through the target tissue so that effective drug concentration should be achieved in the deeper tissues of skin[3]. Clotrimazole is an imidazole derivative having broad spectrum of antifungal activity used orally and topically. It is used to treat candidiasis and yeast infections. Clotrimazole inhibits biosynthesis of ergosterol, resulting in increase in cellular permeability of fungal cell. Clotrimazole may also inhibit endogenous respiration, interact with membrane phospholipids and inhibits the cell membrane by blocking the ion transport pathway[4,5]. The development of a clotrimazole hydrogel may overcome the problems associated with the conventional formulations and also improve the drug penetration to the deeper tissues of skin.

2. Materials and methods.

2.1 Materials

clotrimazole is obtained as a gift sample from Glenmark pharmaceutical, India. Carbopol-934 was procured from S.D. Fine Chemicals Ltd., Mumbai India. Propylene glycol (PG) was procured from Loba Chem Pvt. Ltd., Mumbai India, Methyl paraben and propyl paraben were bought from Himedia Laboratories Ltd., Mumbai India and methanol was bought from Ranbaxy Fine Chemicals Ltd., New Delhi.

2.2. Screening studies

2.2.1. UV absorption Spectra

100 µg/ml solution of clotrimazole was prepared in methanolic water (3:7 v/v) and scanned for UV absorption in the range of 200-400 nm wavelength using UV visible Spectrophotometer (Shimadzu Japan 1601).

2.2.2. Solubility studies

Saturation solubility of clotrimazole was determined in Methanolic water (3:7). Excess amount of drug was added to solvent system, stirred for 30 minutes and left for 48 hours. The solution was then filtered and analyzed spectrophotometrically.

2.2.3. Partition coefficient

Partition coefficient of drug was determined by adding clotrimazole to a separating funnel containing chloroform and water (1:1). Funnel was Shaked properly and left for 24 hours. After 24 hours the 2 phases were separated

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filtered and analyzed using UV Spectrophotometer at 260 nm wavelength.

2.2.4. Standard curve of clotrimazole

From the stock solution the dilutions clotrimazole in concentration of 5 µg, 10 µg, 15 µg, 20 µg, 25 µg, 30 µg, 35 µg and 40 µg were prepared. Dilutions were filtered and absorbance was taken using UV spectrophotometer at 260 nm wavelength.

2.3. Preparation of Hydrogels

Six hydrogel formulations (F1, F2, F3, F4, F5, F6) were developed by dissolving specified amount of clotrimazole (as given in table 1) in suitable solvent system. Weighed amounts of Carbopol-934, PG, and preservatives were dispersed in distilled water, stirred and left overnight. The two solutions were mixed thoroughly and final weight was adjusted. The formed gel was than neutralized by adding sufficient quantity of 1% NaOH solution[6]. The formulations of six hydrogels are given in table (1) below.

Table 1: table for hydrogel formulations

S. No.	Ingredient name	F1 (gm)	F2 (gm)	F3 (gm)	F4 (gm)	F5 (gm)	F6 (gm)
1	Clotrimazole	0.270	0.270	0.270	0.270	0.270	0.270
2	PG	1.0	2.0	3.0	4.0	5.0	6.00
3	Carbopol-934	0.1	0.2	0,3	0.4	0.5	0.6
4	Methanol	1	1	1	1	1	1
5	Methyl paraben	0.058	0.058	0.058	0.058	0.058	0.058
6	Propyl paraben	0.029	0.029	0.029	0.029	0.029	0.029
7	NaOH	0.4	0.8	0.5	0.4	0.4	0.6
8	Water	25	25	25	25	25	25

2.4. Characterization of hydrogels

2.4.1. Determination of pH

pH of each gel formulation was determined using digital pH meter, which was calibrated before use. The pH of gel was determined after diluting and dispersing it in distilled water (10 % w/v).

2.4.2. Spreadability

Spreadability was determined by wooden block and glass slide apparatus. A ground glass slide was fixed on the block and an excess of gel formulation (2g) was placed on it. Gel was sandwiched by using another glass slide which was provided with a hook. Weight of 100 g was placed on the upper slide for 5 minutes to remove entrapped air and to form a uniform thin gel layer between slides. The weight was removed and the excess gel from the edges was scrapped off. Two slides were positioned by fixing to a stand without slightest disturbance and in such a way that only the upper slide can slip off freely by the force of weight tied to it. A 20 g weight was tied to the upper slide carefully. The time taken for the upper slide to travel the distance 6 cm and separate away from lower slide under the direction of weight was noted. Determinations were carried out in triplicate and the mean of three readings was recorded.

Spreadability was calculated using formula:

$$S = ML / T$$

Where, S = spreadability

M = weight tied to upper slide

L = length moved on glass slide

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

2.4.3. Viscosity

The viscosity of hydrogel formulations was determined at room temperature on Brook-field viscometer using spindle no S-06 and the determinations were carried out in triplicate and the average of three readings is recorded.

2.4.4. Drug content

Gel formulations (100 mg was dissolved) in methanol, filtered and volume was adjusted to 100 ml with methanol. Resultant solution was suitably diluted with methanol and absorbance was measured at 260 nm on UV spectrophotometer. Drug content was determined with the help of standard curve of clotrimazole[7].

2.5. In – vitro drug diffusion study

Drug diffusion rate from hydrogel formulations was studied by Franz diffusion cell using cellophane membrane as a barrier. Diffusion membrane was immersed in receptor compartment having methanol-water (3:7) as diffusion medium, maintained at 37 ± 2 ºC for 24 hours to equilibrate. Diffusion cell was placed on magnetic stirrer along with diffusion membrane which separates donor and receptor compartments. Hydrogel 2g was kept on the membrane in donor compartment. The contents of receptor compartment were stirred using magnetic stirrer at 50 rpm. Aliquots each of 3 ml were withdrawn from the release medium at time intervals of 30,60,90,120.150,180,210,240,270,300,360 and420 minutes. Withdrawn samples replaced by equal volumes of fresh medium. Absorbance of these samples was measured by UV spectrophotometer. Cumulative % release from all hydrogel formulations was calculated[8].

3. Results and discussion

3.1. Screening studies

3.2. The drug sample was authenticated on the basis of organoleptic properties, melting point, UV spectra and IR spectra.

3.3. Partition coefficient of clotrimazole

Oil water Partition coefficient of clotrimazole was found to be 5.3.

3.4. Standard curve of clotrimazole

Standard curve of clotrimazole in methanolic water (30:70) was plotted in the concentration range of 5-40 µg/ml. The absorbance of dilutions was taken by UV spectrophotometer at 260 nm wavelength.

The between absorbance and concentration was found linear (R^2 = 0.998) and obeys Lambert's Beer law. Fig (1).

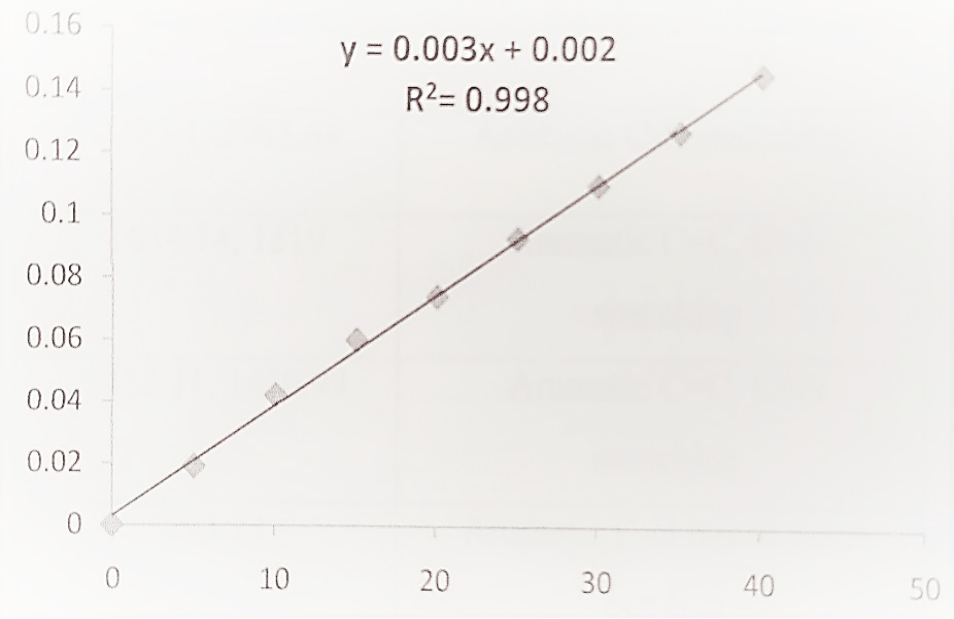

Figure 1: standard curve of clotrimazole

3.5. Characterization of hydrogels

3.5.1. pH determination

Table 2: The pH of all six formulations were in the range of 5.86 – 6.36, which is compatible with skin. pH values are reported in the table below:

Formulation	pH	Formulation	pH
F1	5.86±0.03	F4	6.01±0.10
F2	5.87±0.15	F5	6.03±0.05
F3	6.06±0.15	F6	6.36±0.15

3.5.2. Spreadability

3.5.3. Appropriate values of spreadability were obtained ensuring easy application to skin. The values are reported in table below:

Table 3: Spreadability of hydrogels

Formulation	Spreadability (g.cm/s)	Formulation	Spreadability (g,cm/s)
F1	20.44±0.05	F4	25.05±0.06
F2	18.65±0,16	F5	24.60±0.08
F3	16.63±0.75	F6	23.20±0.06

3.5.4. Viscosity measurement

Viscosity values of all formulations were in the range of 24300 – 48000 cps. Gel with high viscosity do not easily extrude out from tube while less viscous gel may flow quickly. the viscosity of F5 was excellent when compared to other formulations.

Table (4): viscosity of hydrogels

Formulation	Viscosity (cps)	Formulation	Viscosity (cps)
F1	40990	F4	35000
F2	30500	F5	42000
F3	24300	F6	48000

3.5.5. Drug content

Drug content of all six hydrogel formulations was determined. The values are reported in table (5)

Table 5: % drug content in in hydrogels

Formulation	Drug content (%)	Formulation	Drug content (%)
F1	77.28±1.63	F4	83.55±7.04
F2	93.85±1.46	F5	85.30±
F3	89.99±0.29	F6	

3.6. In – vitro drug release study

Drug diffusion study from all six formulations was conducted through cellophane membrane. The results indicate that the hydrogels with high

concentration of propylene glycol has high release rate. The percentage drug release in 6 hours was found to be ranged 59.25±1.15 % to 64.25±2.4 %. F4 formulation showed highest percentage drug release in 6 hours. The percentage release of drug from hydrogels through the membrane at various sampling time of 6 hours were reported in table no (6).

Table 6: drug release from hydrogels

Time	F1	F2	F3	F4	F5	F6
30	6.89±1.73	5.56±1.62	5.41±2.89	5.83±2.33	4.77±1.86	6.66±1.66
60	13.07±1.75	14.89±4.05	9.20±1.17	8.81±2.69	13.53±2.40	13.13±1.95
90	21.09±2.64	21.19±6.9	15.04±1.55	22.2±1.52	17.98±3.68	19.832.73
120	28.29±1.98	24.52±3.30	20.17±1.50	19.18±2.04	22.87±4.36	25.50±3.49
150	33.27±2.70	29.66±4.67	24.57±1.60	33.15±2.30	28.03±4.91	30.44±3.95
180	38.80±3.74	34.23±3.5	30.20±1.63	37.03±2.42	32.15±5.22	35.18±4.62
210	44.14±1.09	38.07±1.51	35.87±1.08	40.96±3.22	35.45±7.09	40.02±3.85
240	51.00±1.00	44.18±6.04	38.82±1.08	45.12±5.94	38.80±6.71	45.22±4.31
270	56.26±0.79	49.32±4.77	43.23±1.35	47.81±6.05	41.61±7.36	48.55±6.04
300	59.03±0.80	53.43±4.06	48.45±1.08	48.84±2.61	45.65±7.92	51.38±5.28
360	61.53±1.31	55.72±4.23	51.74±1.99	59.16±6.23	49.00±7.56	54.45±5.28
420	63.63±1.11	59.38±3.79	61.65±1.12	64.25±2.40	59.25±1.15	59.29±2.50

All values are mean ± SD, n=3

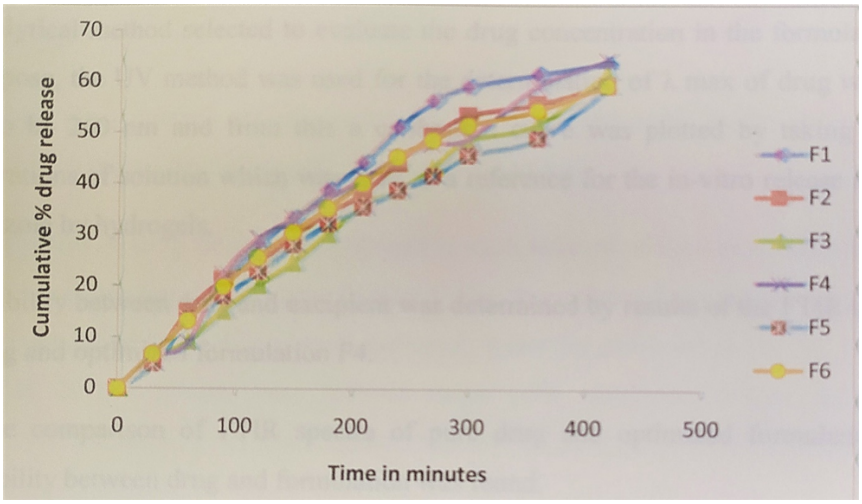

Figure 2: percentage drug release from all 6 hydrogel formulations

3.7. Discussion

To adopt the analytical method, clotrimazole solution in methanolic water was scanned on UV spectrophotometer and maximum absorptivity was fond at 260 nm wavelength. The standard curve showed good linearity and obeys Lambert's Beer law.

The clotrimazole hydrogels were successfully prepared using dispersion method. In this study six formulations were prepared by mixing of Carbopol-934, propylene glycol and preservatives as per formulation table.

All six formulations were evaluated for pH, spreadability, viscosity, drug content and percentage drug release.

pH of all six formulations was found compatible to skin. pH of F4 was found to be excellent when compared to others.

Hydrogel formulations showed good spreadability. Spreadability of F4 formulation was excellent (25.05 gm.cm/s). The viscosity of hydrogel formulations was in the range of 24300-48000 cps. Hydrogels prepared were having good drug content (77.28% - 93.85%).

The percent cumulative drug release of hydrogels at each interval of time were calculated. Good drug release was found from six hydrogels. The order of % cumulative drug release in methanolic water was in order of F4>F1>F3>F2>F6>F5, hence out of all six formulations, F4 showed best % cumulative drug release.

4. Conclusion

In the present study antifungal hydrogels of clotrimazole were successfully formulated by dispersion method. Developed formulations were characterized and F4 was selected as optimized formulation on the basis of pharmaceutical properties and percent drug release.

On the basis of study, it can be concluded that hydrogel for topical delivery of clotrimazole can be successfully developed.

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