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FORMULATION, DEVELOPMENT AND EVALUATION OF FLUCONAZOLE HYDROGEL FOR OPTIMUM ANTIFUNGAL TREATMENT

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ABSTRACT

The present investigation was prepared topical application of hydrogel containing fluconazole was an attempt to make use of the immense potential of hydrogel as a carrier to improve the permeability. In this research it was to developed and evaluated the Hydrogel containing fluconazole to obtain the optimized formulation which favorable for application as skin delivery system. Fluconazole is used for the treatment of local and systemic fungal infection. But one of the major problems for efficient drug delivery is low penetration rate of fluconazole due to its high solubility and low permeability. The hydrogel of fluconazole was prepared by cold method and evaluated. Gel was evaluated for their clarity, pH, viscosity, spreadability, studies using standard procedure. In vitro release of GF5 formulation was higher than the marketed gel. Based on r^2 the GF5 formulation followed Higuchi model for the mechanism of drug release.

Keywords: Antifungal activity, Hydro gel, Fluconazole.

INTRODUCTION

Topical administration is the application of a localized drug delivery systems anywhere in the body through rectal, ophthalmic, skin, and vaginal as topical routes. Skin is one of the most readily accessible organs on the human body for topical administration and is the main route of the topical drug delivery system.

Fungal infections traditionally have been divided into two distinct classes: systemic and superficial. Subsequently, the significant antifungal agents are classified into tropical drugs. Antifungal drugs are classified by their chemical design as polyene antifungals, azole antifungals, allylamine antifungals, echinocandin antifungals, and others [1-2].

The major classes of effective topical antifungal gel are polyenes, azoles, and allylamine/benzylamines. Presently, these antifungal medications are commercially conventional dosage forms like creams, gels, moisturizers, and sprays. The effectiveness of the skin antifungal treatment depends upon the penetration of drugs through the targeted tissue. Subsequently, the effective concentration of drugs should be accomplished in the skin.

Delivery of antifungal compounds into skin can be enhanced with the carriers including colloidal systems, vesicular carriers, and nanoparticles. Present study is planned to developed evaluate fluconazole antifungal hydrogel formulation [3-8].

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 In recent years scientific and technological advancements have been made in the research and development of hydrogel drug delivery systems by overcoming physiological adversities such as first-pass metabolism and for improved local action [9].

Several approaches are currently utilized to treat pain, inflammation, skin diseases, for disinfection of skin, and as controlled release devices in the field of the wound dressing. Research studies were carried out on the formulation of transdermal gels of anti-fungal agents by using various polymers. The present investigation includes the formulation of transdermal gels of Fluconazole by using polymers of natural and semi-synthetic origin.

MATERIALS AND METHOD

Material

Fluconazole and Ethyl cellulose was procured as gift sample from Euphoria Healthcare Pvt. Ltd. Mumbai, Maharashtra., Dichloromethane, Polyvinyl alcohol, Carbopol 934 were procured from Merck material Pvt. Ltd., Mumbai, Maharashtra. All the reagents and solvents were used analytical grade.

Formulation development of hydrogel of Fluconazole

Preparation of fluconazole hydrogel by emulsion solvent diffusion method the organic phase consists of the accurately weighed amount of fluconazole and ethyl cellulose dissolved in dichloromethane. The aqueous phase which consists of polyvinyl alcohol dissolved in warm water was used as the emulsifying or stabilizing agent. The organic phase was gradually added into an aqueous phase and stirred mechanically at 1200 rpm for 2 hrs at room temperature to remove the solvent dichloromethane from the mixture. Accurately weighed amount of carbopol

934 was taken and soaked in water for 24hrs for complete swelling of the polymer. To the weighed amount of carbopol gel base Propylene glycol was added as a penetration enhancer. Hydro gel formed were filtered and dried at room temperature and stored in a tightly closed container [10].

Table 1:- Composition of Fluconazole Hydro gel by emulsion solvent diffusion method

Ingredients	GF1	GF2	GF3	GF4	GF5	GF6	GF7	GF8	GF9
Fluconazole (mg)	100	100	100	100	100	100	100	100	100
Ethyl cellulose (g)	0.15	0.2	0.25	0.3	0.15	0.2	0.25	0.3	0.3
Dichloromethane (ml)	20	20	20	20	20	20	20	20	20
Polyvinyl alcohol (% w/v)	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3
Carbopol 934(g)	1	1	1	1	1	1	1	1	1
Propylene Glycol(ml)	1	1	1	1	1	1	1	1	1
Water (ml)	20	20	20	20	20	20	20	20	20

Evaluation of gel

Gel was evaluated for their clarity, pH, viscosity, spreadability, studies using standard procedure. All studies were carried out in triplicate and average values have been reported

Rheological Characteristic: -

The rheological characteristics were studied for topical gel formulations like color, viscosity etc.

Consistency of gel: - It was measured by Penetrometer. Three containers were filled carefully and completely with formulation, without forming air bubbles and stored at 25±0.5^{0}C for 24 hrs. Test samples were placed on Penetrometer and position of spindle was adjusted as such that, its tip just touches the surface of sample. Penetrating object was released for 5 sec. Depth of penetration was measured. Same was repeated with remaining formulation[11-12].

Washability: - Formulations were applied on the skin and then observed for it removal after ease washing with water.

Extrudability study: - The gel formulations were filled into aluminum collapsible tubes. The tubes were pressed by applying weight to extrude the material. Weight was measured which required to extrude the gel from collapsible tubes.

Spreadability Principle: - An important criterion for gel is that it must possess good spreadability. Spreadability is a term expressed to denote the extent of area to which the gel readily spreads on application to skin. The therapeutic efficacy of a formulation also depends on its spreading value[13-14].

A special apparatus has been designed to study the spreadability of the formulations. Spreadability is expressed in terms of time taken to slip a movable slides from another fixed slide placed in a frame with formulation under the application of a certain load. Lesser the time taken for the separation of two slides, better the spreadability.

pH of gel was determined by digital pH meter. One gram of gel was dissolved in 25 ml of distilled water and the electrode was then dipped in to gel solution for 30 min until constant reading obtained. And constant reading was noted. The measurements of pH of each formulation were replicated three times.

Viscosity: - The viscosity of the prepared gel was determined using Brookfield digital viscometer. The viscosity was measured using spindle no. 6 at 30 rpm at ambient room temperature 37^0C. The sufficient quantity of gel was filled in appropriate wide mouth container. Wide mouth container use to allow spindle of the Viscometer inside of the container. Viscosity value was noted down after stable of reading. Samples of the gel were allowed to settle over 30 min at the constant room temperature before the measurements[15-16].

***In-vitro* drug release studies using the prehydrated cellophane membrane: -**

Preparation of cellophane membrane for the diffusion studies: -

The cellophane membrane approximately 25 cm x 2cm was taken and washed in the running water. It was then soaked in distilled water for 24 hours, before used for diffusion studies to remove glycerin present on it and was mounted on the diffusion cell for further studies.

The *In-vitro* diffusion of drug from the different gel preparations were studied using the classical standard cylindrical tube fabricated in the laboratory; a simple modification of the cell is a glass tube of 15mm internal diameter and 100 mm height. The diffusion cell membrane was placed with one gram of the formulation and was tied securely to one open end of the tube, the other end was kept remain open. The cell was inverted and immersed slightly in 250 ml of beaker containing freshly prepared phosphate buffer pH 7.4, as a receptor media and the system was maintained for 2 hrs at 37± 0.5^o C. The media was stirred using magnetic stirrer. Aliquots, each of 5 ml volume were withdrawn periodically at predetermined time interval of 15, 30, 45, 60, 90, 120 min and replaced by an equal volume of the receptor medium. The aliquots were suitably diluted with the phosphate buffer pH 7.4 and analyzed by UV-Vis spectrophotometer at 233.0 nm for Fluconazole[17-18].

Stability studies Stability studies of optimize formulation of gel :- gels were packed in aluminum collapsible tubes and subjected to stability studies at 40±2°C/75±5% RH and 30±2°C/60±5% RH as per ICH guidelines for a period of 3 months. Samples were withdrawn at 1 month time intervals and evaluated for physical appearance, pH, rheological properties, drug content and *in vitro* drug release [19].

RESULTS AND DISCUSSION

pH of Gel

The pH of the gel formulations containing Fluconazole was determined by pH meter and found in the range of 6.5 to 7.0 which lies in the normal pH range of the skin.

Viscosity of Gel

The viscosity of the prepared gel containing Fluconazole was determined by Brookfield viscometer using spindle number 7 at different rotation speed. At each speed, the corresponding dial reading was noted. The gel formulations containing Fluconazole formulated with using different concentration and the viscosity was found respectively for GF1, GF2, GF3, GF4, GF5, GF6, GF7, GF8 and GF9 formulation.

Spreadability of Gel

The values of spreadability indicated that the gels were easily spreadable by applying low shear force. Spreadability of gel formulation of Fluconazole was found 15.21±2.1, 14.56±0.21, 14.44±2.87, 13.56± 2.45, 13.35±2.5, 12.15±0.42, 11.25±1.35, and 11.05±2.5, 10.15±2.45 respectively for GF_1, GF_2, GF3, GF_4, GF_5, GF_6, GF_7, GF_8, and GF9.

Drug Content of Gels

The drug content of and loaded gel was found to be more than 97% for all the formulations. Drug content for fluconazole containing gel formulations was 98.32±0.25, 98.59±0.35, 98.63±0.45, 98.75±0.35, 98.45±0.32, 98.58±0.21, 98.63±0.12, 98.98±0.4, and 98.15±0.4 respectively for GF_1, GF_2, GF_3, GF_4, GF_5, GF_6, GF_7, GF_8, GF_9 formulation.

Extrudability of Gel

Extrudability in the case of both the drug containing gel formulation was found to be good with moderate. As the concentration of these substances were increased then it consistency and viscosity were also increased and resultant the poor extrudability of gel.

Drug release kinetics with model fitting of Fluconazole gel:-

These values of in-vitro release were attempted to fit into various mathematical models, plot of zero order, first order, higuchi matrix and Korsmeyer-Peppas. These values were compared with each other for model fitting equation. Based on the highest regression values (r), the best fit model for all the formulations was zero order

release kinetics. Further Korsmeyer-Peppas equation resulted into the values of n > 1, which appears to indicate that the release from the prepared optimized gel formulation (GF5) follows Higuchi order release Kinetics.

Table 2: Characterization of formulations G_{F1} to G_{F9}

Parameters	Formulation								
	GF1	GF2	GF3	GF4	GF5	GF6	GF7	GF8	GF9
Physical Appearance	Translucent, white, smooth on application	Translucent, white, smooth on application	Translucent, white, smooth on application	Translucent, white, smooth on application	Translucent, white, smooth on application	Translucent, white, smooth on application	Translucent, white, smooth on application	Translucent, white, smooth on application	Translucent, white, smooth on application
pH	6.98±0.2	6.82±0.2	6.98±0.3	6.85±0.4	6.95±0.3	6.85±0.1	7±0.3	7.03±0.2	7.03±0.2
Viscosity (CP)	30145±8.9	30989±10.2	31547±12.5	32569 ±3.6	32458±4.5	32569±10.5	33568±10.1	34548±2.5	34987±4.2
Spreadability (gm.cm/sec)	15.21±2.1	14.56±0.21	14.44±2.87	13.56± 2.45	13.35±2.5	12.15±0.42	11.25±1.35	11.05± 2.5	10.15± 2.45
% Drug content	98.32±0.25	98.59±0.35	98.63±0.45	98.75±0.35	98.45±0.32	98.58±0.21	98.63±0.12	98.98±0.4	98.15±0.43
Extrudability	+++	+++	+++	+++	+++	+++	+++	+++	+++

***Average of three determinations (n=3±SD)**

Table 3: In-*vitro* drug release studies of G_{F1} to G_{F9} formulation

S. No.	Time (min)	% Cumulative drug release								
		G_{F1}	G_{F2}	G_{F3}	G_{F4}	G_{F5}	G_{F6}	G_{F7}	G_{F8}	G_{F9}
1	0	0	0	0	0	0	0	0	0	0
2	15	16.58	18.78	19.87	24.14	26.45	31.89	36.56	38.89	43.56
3	30	37.56	41.25	44.56	54.48	59.78	67.98	73.56	76.65	81.56
4	45	45.89	53.56	54.54	64.56	74.14	81.45	89.14	98.78	98.56
5	60	53.69	58.87	60.25	69.74	83.45	96.65	98.87	98.25	99.45
6	90	65.89	74.48	83.56	88.47	93.69	97.89	98.98	99.45	99.98
7	120	80.12	86.56	94.56	95.54	99.87	98.89	99.78	99.98	99.98

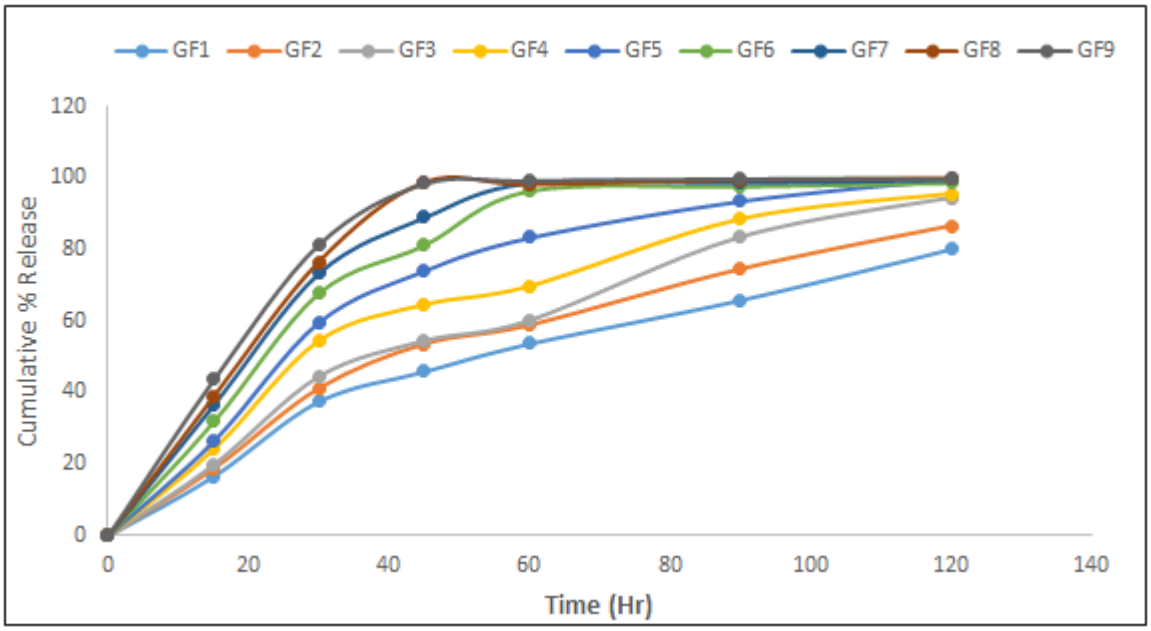

Figure 1: In-*vitro* drug release studies of G_{F1} to G_{F9} formulation

Stability Study:-

Stability studies for prepared gels were conducted at 40±2°C/75±5% RH and 30±2°C/60±5% RH as per ICH guidelines for a period of 3 months. Results of stability studies clearly indicates that optimized batches gel GF5) were stable over the chosen temperature and humidity conditions up to 3 months as were found no significant variation in drug release from these formulation.

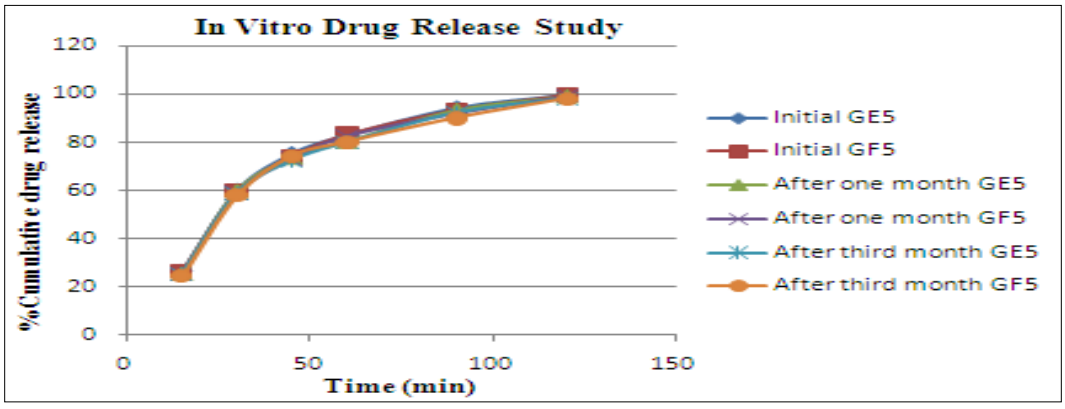

Figure 2: *In-vitro* drug release study

CONCLUSION

Nine formulation of gel were prepared nine formulations of Fluconazole and nine formulations of as model drug. Gel of Fluconazole and prepared by using by emulsion solvent diffusion method. Result shows that the physical appearances of the gel formulations were translucent, white and smooth on application. Release of drug from gel base was significantly slower, which confirmed that slight prolonged drug release rate. Incorporation of rice bran wax affected the release rate of the drug. By increasing the amount of, the release rate of the drug decreased, which could be related to the increased rigidity of the formulation, followed by its decreased permeability for the drug.

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