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PREPARATION AND EVALUATION OF HYDROGEL CONTAINING FLUCONAZOLE FOR ANTIFUNGAL PROPERTIES

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ABSTRACT

Fluconazole is an imidazole derivative used for the treatment of local and synthetic fungal infection. The oral use of fluconazole is not recommended as it has many side effects. In order to decrease the side effects, fluconazole hydrogel have been developed. Topical gel preparations are intended for skin application or to certain mucosal surfaaces for local action or transdermal penetration of medicament or for their emollient or protective action. Topical delivery of drugs can be achieved by incorporating drug into the gel matrix for effective delivery of drugs, thus avoiding first pass metabolism and for increased local action in skin diseases. The present study was designed to formulate and evaluate different formulae of hydrogel gel containing fluconazole for treatment of fungal infection of skin. The gel was formulated by using carbapol and Tween 80 as gelling agent. Five different formulae (ME1 to ME5) was prepared and characterized physically in term of colour, spreadability, pH and rheological properties (viscosity), skin irritation studies, mechanical stress study and drug release. Drug-excipients compatibility studies were confirmed by FT-IR. These results suggest the feasibility of the topical gel formulation of fluconazole.

KEYWORDS: Fluconazole, Hydrogel, Antifungal properties, Spreadability, Carbapol 940, Tween 80.

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. Among the topical formulation clear transparent gels have widely accepted in both cosmetics and pharmaceuticals.[1] Topical treatment of dermatological disease as well as skin care, a wide variety of vehicle ranging from solids to semisolids and liquids preparations is available to clinicians and patients. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparation.[2] For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, cream, gel, ointments, liquids, aerosols and injectables, as drug carriers. Delivery of drugs to the skin is an effective and targeted therapy for local dermatological disorders. This route of drug delivery has gained popularity because it avoids first pass effects, gastrointestinal irritation, and metabolic degradation associated with oral administration. Due to the first past effect only 25-45% of the orally administered dose reaches the blood circulation. In order to bypass these disadvantages the gel formulations have been proposed as topical application. Gels are defined as "semisolid system in which a liquid phase is constrained within a polymeric matrix in which a high degree of physical and chemical cross-linking introduced". Fluconazole is a synthetic antifungal agent of the imidazole class; it works by slowing the growth of fungi that cause infection. It is used to treat fungal infection. Triazole drug targets the fungal-specific synthesis of membrane lipids. Fluconazole inserts preferentially into fungal membranes and disrupts their function. 5-fluorocytosine targets fungal specific DNA replication.[3] Hydrogel based drug delivery system is a most promising novel approach now-a-days for delivery of drug for extended period of time. Hydrogel are the three-dimensional network polymers that swell in aqueous solutions and in swollen state, these become soft and rubbery, resembling a living tissue and some possess excellent biocompatibility. Hydrogel systems possesses a good stability in surrounding conditions like change in pH, ionic strength, temperature and frequent changes of environment in the GI-tract, which has a variation of environment from the stomach to intestine.[4] Hydrogel from natural polymers, especially polysaccharides have been widely used for their advantages over synthetic polymers such as non-toxic, biocompatible, biodegradable, freely available, able to modify the properties of aqueous environment, capable of thicking,

emulsify, stabilize, encapsulate and swell and to form gels films. But they can be modified to overcome some drawbacks, like uncontrolled rate of hydration, microbial contamination, drop in viscosity on storing, etc.[5] In present work, attempt was made to formulate and evaluate topical hydrogel drug delivery systems. Attempts were made to enhance drug absorption and exposure to improve therapy by controlling the rate of drug release from dosage forms. Rate of drug release was modified using gelling or thickening agents. The ultimate aim was to improve bioavailability of the drug and to improve the market formulation by the use of combination of hydrophilic polymers.

MATERIALS AND METHODS

Materials

Fluconazole was obtained as a gift sample from Yarrow Chemical Ltd, Bombay. Carbopol- 940 (Loba Chemie Pvt. Ltd., Mumbai, India), Tween 80 (Qualigens Fine Chemicals, Mumbai, India), sodium hydroxide (Prime laboratories, Hyderabad), potassium dihydrogen phosphate (Alpha Chemika, Maharashtra, India) were procured and used in this investigation. All other chemicals used were of analytical grade and were used without any further chemical modification.

Preformulation studies

FT-IR spectroscopy

Identification of drug FT-IR spectroscopy method was used for the identification and evaluation of drug and excipients. Drug KBR pellets were used to record the FT-IR spectrum with a Perkin-Elmer model.

Determination of λ_{max} of Fluconazole

The content fluconazole in was estimated by UV spectrophotometer technique which is based on the measurement of absorbance at wavelength 275 nm in phosphate buffer medium at pH 7.4. The technique was validated for its accuracy and precision. The method obeyed Beer's law in the concentration range 0-25 µg/ml. In observation (n=6), the mean error (accuracy) and relative S.D. (precision) were found to be 0.6% & 1.2% respectively.

Formulation of fluconazole topical hydrogel

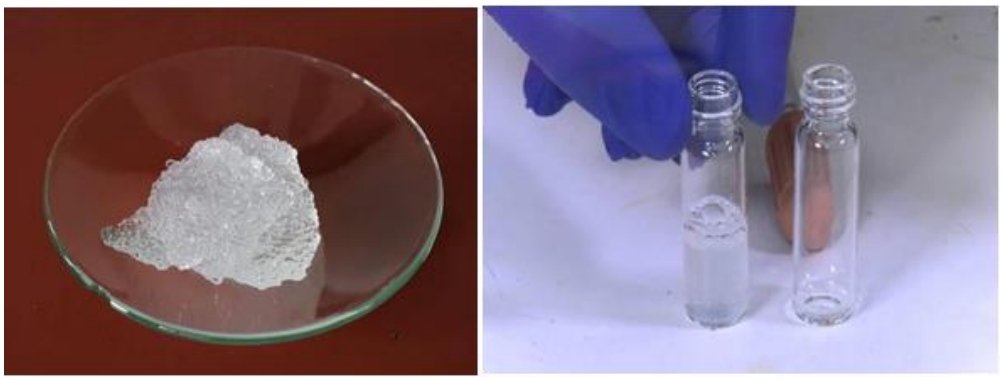
The hydrogel is composed of mainly three ingredients. tween 80, and carbopol 940. Usually it is made up of two phases, first oleic acid and tween 80 (oil phase) and second water and carbopol 940 (aqueous phase), i.e. hydrogel is combine with oil phase made up of oleic acid and tween 80. For the preparation of hydrogel firstly we take carbopol and kept it 4 hrs for swelling then stand the procedure of formulation. For preparation of hydrogel used the drug as active ingredient, carbopol-940 as gelling agent and other excipients were used. Firstly added 15ml of oleic acid with 9.5ml of tween 80 with continuous stirring at room temperature on 500 rpm then after 1 hr of continuous stirring added 10 mg of fluconazole in it. Then again wait for 1 hr and now added 4ml of water (drop by drop) with 50 mg of fluconazole. Then added carbopol-940 that had been swelled from last 4 hrs now leave it for another 3 to 4 hr on magnetic stirrer and kept it aside for 24 hr for proper gel formation and fluconazole is ready.[6,7]

Evaluation of hydrogel[8,11]

Physical evaluation: Gels were visually checked for colour, odour, consistency and homogeneity.

pH measurement: The pH of prepared gels was determined using a digital pH meter, which was calibrated before each use with standard pH solution. Each formulation wasfound in an oral cavity pH range (6.8-7.2).

Viscosity: Viscosities of all 8 formulated gels were measured by using Brookfield viscometer at 100 rpm using spindle number 64. Viscosities were recorded at room temperaturefor all formulations.



Viscosity measurements

Comparative Viscosity values of Formulations

Formulations	Viscosity(cps)*
ME-1	52.6±0.6
ME-2	75.3±0.8
ME-3	91.4±0.4
ME-4	103.5±0.5
ME-5	118.2±0.2

***Values are mean** ±SD, n=3

Spreadibility: Two equal sized glass plates were taken and about 1 gm of gelwas placed into a circle of 1 cm diameter marked on a graph paper which was placed billow a glass plate, over which a second glass plate was placed. A weight of 100 g was allowed to reston the upper glass plate and increase in a diameter due to the spreading of the gels was noted. Spreadability was determined using following formula. S=ML/T.

Drug release study: An in-vitro drug release study was carried out using Franz's Diffusion cell (Dolphin) and egg membrane. An egg membrane was stored in phosphate buffer (pH 6.8) for 24 hrs before use. Egg membrane was tied to one end of donor compartment and the receptor compartment was filled with the phosphate buffer of 6.8 pH and temperature was maintained at 37 ±0.5°C with constant stirring. 1 gm of gel was placed on a donor compartment. The 1 ml samples was collected from the receptor compartment at predetermined time interval and replaced by equal volume of phosphate buffer to maintain a sink condition throughout the experiment. The amounts of drugs in the sample were assayed by using UV-Vis spectrophotometer (Shimadzu-1900) at 210 and 410 nm.

S No.	Time (min)	Percent DrugRelease of Fluconazole
1	0	0
2	15	5.71750285
3	30	12.56385405
4	45	18.1559293
5	60	23.89338654
6	90	29.4541049
7	120	35.03762828
8	180	40.54703535
9	240	46.07354618
10	300	51.37725199

In-vitro diffusion studies

Skin (abdomen) of swiss albino male mice was taken for diffusion procedures. Mice (30-35g) were anesthetized slightly by di-ethyl-ether and hairs were removed from the skin of mice. They were sacrificed and the abdominal skin of mice was taken off. After removing the subcutaneous fat the skin was washed and checked for its integrity. The skin was stored in a refrigerator at 4°C overnight andthen used for the evaluation. The diffusion procedures were performed in a diffusion cell with a recirculating water bath with 12 diffusion cells. The skin was stretched and fixed between the donor and the receptor chamber of diffusion cells. The cell has an effective diffusion area of 2.8 cm^2 and 7ml volume of cell. The receptor chamber was filled with freshly prepared mixture of water ethanol in the ratio of 4:1 v/v to solubilize and fluconazole. The solution of 20% ethanol was used to solubilize and fluconazole. The receptor chambers were thermostat at 37°C and the solution in the receptor chambers was stirred (continuously) at 300 rpm. The formulation (1.5 g) containing and fluconazole was kept in the donor chamber. At appropriate time interval, 0.5 ml of the solution from receptor chamber was removed for UV evaluations and replaced immediately with the same volume of freshsolution of ethanol (20%). The cumulative amount of drug diffused through mice skin was plotted against time.

Skin irritation studies

A set of 8 rats was used for studying skin irritation test. The hydrogel was applied on the shavenskin of rats. The undesirable skin changes i.e., change in colour, scratches and change in morphology were determined within 24 hours of application.

Table 1: Spectrum of activity for antifungal drugs.

	Fluconazole
C. albicans	++
C. dubliniensis	++
C. tropicalis	++
C. glabrata	+/-
C. krusei	-
C. parapsilosis	++
C. guilliermondii	+
C. lusitaniae	++

Mechanical stress study

The following gel demonstrates the mechanical stress study of different formulations developed. The highest % phase separation was recorded as 10 after exploring 60 minutes centrifugation time. The minimum % phase separation was noted as 2 after 10 exploring 10 minutes centrifugation time.

CONCLUSION

The Fluconazole hydrogel for topical application was formulated using tween 80 and carbopol 940 and evaluation tests were performed. Proper selection of polymers and their proportions is a prerequisite for designing and developing a transdermal drug delivery system. The formulated gels showed good homogeneity, good stability and better drug release rates when compared to marketed formulation.

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