



Research Paper

Ketoconazole Derma Sticks For Topical Applications

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Abstract-*The topical drug delivery systems available for the treatment have several disadvantages like greasiness, inconvenient to store and requires applicator or use of fingertip, which may lead to contamination. Therefore, it was found essential to find an alternative to counter all the above disadvantages effectively and hence in the present work, formulation and development of medicated sticks has been planned with the drug, Ketoconazole that has anti bacterial and anti fungal activity. In order to formulate an effective and efficient topical preparation, consideration must be given to the intended purpose. This is directly concerned with the site of action and the desired effect of the preparation. The most common form of chromomycosis is known as chromoblastomycosis or verucous dermatitis the lesions consist of warty cutaneous nodules which resemble the florest of cauliflower. The disease is usually confined to the subcutaneous tissue of the feet and lower legs. The topical drug delivery systems available for the treatment have several disadvantages like greasiness, inconvenient to store and requires applicator or use of fingertip, which may lead to contamination. Therefore, it was found essential to find an alternative to counter all the above disadvantages effectively and hence in the present work, formulation and development of medicated sticks has been planned with the drug, Ketoconazole that has anti bacterial and anti fungal activity. The preparation and characterization of medicated sticks was carried out in different phases. Phase I studies includes preparation and evaluation medicated derma sticks using the ointment bases with varied concentrations of waxes and incorporation of medicament in the optimized formula by heating and congealing process. Phase II studies includes characterization of prepared medicated sticks for weight variation, thickness, length, size, shape and drug content uniformity. Phase III studies involves in vitro drug diffusion studies by using prehydrated cellophane membrane for 160 minutes in pH 7.4 phosphate buffer. Phase IV studies includes anti microbial studies of prepared formulations by cup plate method. Phase V studies includes Stability studies conducted for a period of 3 weeks and FT-IR Spectral analysis conducted. Phase VI studies includes Primary skin irritation studies carried out on rabbits and guinea pigs and in healthy human volunteers showed no sensitization and edema on skin after 72 hrs of application. The results of present study revealed that the prepared medicated sticks of Ketoconazole are convenient, equally effective, without any contamination chances on application and free from skin irritation.*

Keywords: Ketoconazole, medicated sticks, Dermatitis.

Introduction

The topical drug delivery systems available for the treatment have several disadvantages like greasiness, inconvenient to store and requires applicator or use of fingertip, which may lead to contamination. Therefore, it was found essential to find an alternative to counter all the above disadvantages effectively and hence in the present work, formulation and development of medicated sticks has been planned with the drug, Ketoconazole that has anti

bacterial and anti fungal activity ^[1,2]. Formulation of an effective and efficient topical preparation is the need of the hour and consideration must be given to the intended purpose. This is directly concerned with the site of action and the desired effect of the preparation. The most common form of chromomycosis is known as chromoblastomycosis or verucous dermatitis the lesions consist of warty cutaneous nodules which resemble the florest of cauliflower.

Many patients express difficulty in application of ointments, creams, gels etc. results in non-compliance and ineffective therapy. Recent advance in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for application and to achieve better patient compliance. One such approach is medicated sticks^[3,4]. An advantage of this drug delivery system includes patient compliance, convenience and comfort for efficient treatment include application without fingertip, immediate onset of action, reduced dosage regimen and economy. Clotrimazole^[5,6] that has anti bacterial and anti fungal activity commonly used in the treatment of several skin disorders not available in such dosage form^[7,8]. Objective of the present work was to develop a NDDS of Ketoconazole prepared by heating and congealing method a convenient model to use by patients.

Materials and Methods

Ketoconazole was gift sample from S.D. Fine Chemicals Ltd., Mumbai. Stearyl alcohol pure, white petrolatum (Loba Chemie Pvt. Ltd., Mumbai), Sodium lauryl sulphate, Propylene glycol (Ranbaxy lab. Ltd., SAS Nagar), Methanol (Qualigens Fine Chemicals, Mumbai) were used.

Preparation of Ketoconazole stick: Medicated dermasticks of Ketoconazole were prepared by heating and congealing according to the formula (Table 1). Depending upon the weight, thickens and length of medicated derma sticks, the formulae was chosen for the incorporation of the drug. Stearyl alcohol^[9, 10] and white petrolatum was melted in a china dish and heated this mixture upto 70°C. Dissolved sodium lauryl sulfate, propylene glycol in purified water and heat the solution to 70°C separately. Added the oleaginous phase slowly to the aqueous phase, stirring constantly and then the drug was added slowly with continuous stirring in order to get a uniform mixture in optimized formulation. The hot mixture was poured into the glass mould and cooled to get the desired shape of sticks. The stick was removed from the mould after 24 hours with the help of plunger and inserted into the medicated derma stick container.

Evaluation of Dermasticks: Three sticks were selected randomly and weighed individually. The individual weights were compared with the average weight for determination of weight variation. As the shape of the stick is cylindrical the thickness and length was determined with the help of screw gauge and vernier calliper respectively. The average thickness was measured, by observing thickness at three different parts of the stick. For drug content uniformity the stick equivalent to 50 mg of drug was extracted with methanol and liquid was filtered. The Ketoconazole content was determined by measuring the absorbance at 231 after appropriate dilution with methanol. The drug content was calculated using the standard calibration curve. The mean percent was calculated as an average of three determinations. IR spectra of Ketoconazole and its excipients of the formulations were obtained by KBr pellet method using Perkin-Elmer FTIR series (Model-1615) spectrophotometer in order to rule out drug carrier interactions.

In vitro drug diffusion studies:^[11] *In vitro* drug diffusion of prepared Ketoconazole dermasticks were studied using permeation cell which is made up of a glass cylinder with both ends open, 10 cm height, 3.7 cm outer diameter and 3.1cm. inner diameter. A cellophane membrane soaked in distilled water (24 hrs. before use) was fixed to the one end of the cylinder. Stick containing one gram of Ketoconazole was taken in the cell (donor compartment), then the cell was immersed in beaker containing 100 ml of drug free pH 7.4 phosphate buffer^[12,13] (receptor compartment). The cell was immersed to a depth of 1 cm. below the surface of the receptor fluid. The medium in the receptor compartment was agitated using a magnetic stirrer and a temperature of 37°C ± 1°C was maintained. Samples (5 ml) of the receptor compartment were withdrawn at specified intervals over a period of 160 min and analyzed for drug content by measuring the absorbance at 231 nm. The volume of sample withdrawn at each interval was replaced with a fresh quantity of diffusion medium. Cumulative percent of Ketoconazole released was calculated and plotted against time.

Anti microbial studies of prepared formulations: The anti microbial studies were carried out for the prepared formulations by cup-plate method using *Candida Albicans* as test organism. The cultures of *Candida albicans* were cultivated on Sabouraud's dextrose agar maintained on slants in the refrigerator (4±2°C).

Cup-plate method: The composition of Sabouraud's dextrose agar was taken in a 250 ml of conical flask and was dissolved in 100 ml of distilled water. The pH was adjusted to 5.6. The medium was sterilized in an autoclave at 15 lbs for 20 minutes. After the completion of sterilization, the medium was kept aside at room temperature. 0.5 ml diluted suspension culture in NaCl 0.9% were added to 100 ml of medium at 47±2°C and used as inoculated layer. The medium (20 ml) was poured into a sterilized petridish to give a depth of 3-4 mm, and was assured that the layer of medium is uniform in thickness by placing petridish on a leveled surface. After solidifying the medium at room temperature, with the help of a sterile cork borer, cups of each 6 mm diameter were punched and scooped out from the petridish. Using sterile pipettes sample solutions (0.1 ml) of known concentration were fed into the cup. The petridish was then incubated for 24 hours at 37°C. After incubation the zone of inhibition was measured (Table 4).

Preclinical studies: Primary skin irritation test in animals: This test is conducted on 3 healthy rabbits and guinea pigs (2 male and 1 female), which were fed with fresh food and water during the test period. 24 hours prior to test, the hair from the lower abdominal portion was shaved to expose sufficiently large test area. The test site was cleaned with surgical spirit then medicated stick is applied to test area. The test site was observed for erythema and edema for 72 hrs. after application. This test was conducted to evaluate the irritancy of the prepared medicated stick on the intact skin of rabbits and guinea pigs.

Preclinical studies: Primary skin irritation test in healthy human being beings: 3 Healthy Human Volunteers were selected for the study for each formulation. The test

site was cleaned with surgical spirit then medicated stick is applied to test area. The test site was observed for erythema and edema for 24 hrs, 48 hrs. and 72 hrs after application. This test was conducted to evaluate the irritancy of the prepared medicated stick on the intact skin. None of the prepared medicated sticks showed any erythema or edema, indicating that the prepared formulations were non-irritant on the skin. (Table 5, 6, 7). These studies were carried out under the guidance of qualified dermatologists with the permission of ethical committee of M. R. Medical College, Gulbarga.

Stability Studies: Short-term stability studies for all the formulations prepared were carried out by storing at $27 \pm 2^\circ\text{C}$ for a period of three weeks. At intervals of one week the sticks were visually examined for drug content uniformity and any physical change.

Results and Discussion

Medicated sticks of Ketoconazole were prepared by heating and congealing method using Stearyl alcohol as stiffening agent while petrolatum used as emollient, propylene glycol and sodium lauryl sulphate were used as humectants and emulsifying agent respectively. A total of six formulations were designed. As the material was uniformly filled in mould with uniform length and diameter, the sticks obtained were of uniform length, thickness and weight respectively. The drug content was found to be 95.26 to 99.40 % (Table 2). Among the formulations, various concentrations of Stearyl alcohol (15 to 25% w/w) was employed as stiffening agent. The *in vitro* drug diffusion was carried out for all the formulations i.e. KL1 in pH 7.4-phosphate buffer over a period of 160 minutes (Table 3). The data reveals that overall, formulation KL1 showed the maximum 70.23% of drug release in 160 minutes as compared to other formulations. IR spectroscopic studies indicate that the drug is compatible with all the excipients. The IR spectra showed all the characteristic peaks of pure drug, thus confirming that no interaction of drug observed with the component of the formulations (Figure 1, 2). Antimicrobial studies revealed that the drug in formulation show equal zone of inhibition like pure drug (Figure 3). The preclinical studies in animals and healthy human volunteer

revealed that the prepared formulations will be safe to use for topical applications (Table 4).

Conclusions

The present work is a unique piece of contribution to the drug industry. The results will be useful to industry R&D for further investigations. The continuation of this work clinical studies is in progress.

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Table 1: Formulation of medicated derma stick (KL 1)

Sl. No.	Ingredients	Quantity in Gms.
1.	Drug	15.00
2.	Stearyl alcohol	15.00
3.	White petrolatum	20.00
4.	White Beeswax	5.00
5.	Sodium lauryl sulfate	1.50
6.	Propylene glycol	12.50
7.	Purified water	45.00

Table 2: Characterization of prepared medicated derma sticks

Formulation code	Medicated Stick		
	Weight (gm)	Thickness (mm)	Length (cm)
	Mean \pm SD	Mean \pm SD	Mean \pm SD
KL - 1	1.61 \pm 0.02	6.62 \pm 0.02	4.0 \pm 0.01

* Each reading is a mean of three determinations

Table 3: In vitro Drug Release of Ketoconazole Dermastick (KL 1)

S. No.	Time (min)	Square root of time (min)	log time	% Cum. drug released*	Log % cum. drug released	% Cum. drug remaining	Log % cum. drug remaining
1	00	0.000	0.000	0.00 ± 0.00	0.000	00.00	2.000
2	20	4.472	1.301	3.70 ± 0.13	0.568	96.30	1.984
3.	40	6.324	1.602	19.71 ± 0.17	1.295	80.29	1.905
4.	60	7.745	1.778	23.75 ± 0.25	1.376	76.25	1.882
5.	80	8.944	1.903	30.91 ± 0.36	1.490	69.09	1.839
6.	100	10.000	2.000	42.58 ± 0.47	1.629	57.42	1.759
7.	120	10.954	2.079	47.71 ± 0.68	1.679	52.29	1.794
8.	140	11.832	2.146	58.98 ± 0.72	1.771	41.05	1.613
9.	160	12.649	2.204	70.23 ± 0.91	1.847	29.77	1.473

* Each reading is a mean of three determinations

* One gm of sample contains 15 mg. of drug.

Figure 1: IR SPECTRA OF KETOCONAZOLE (PURE DRUG)

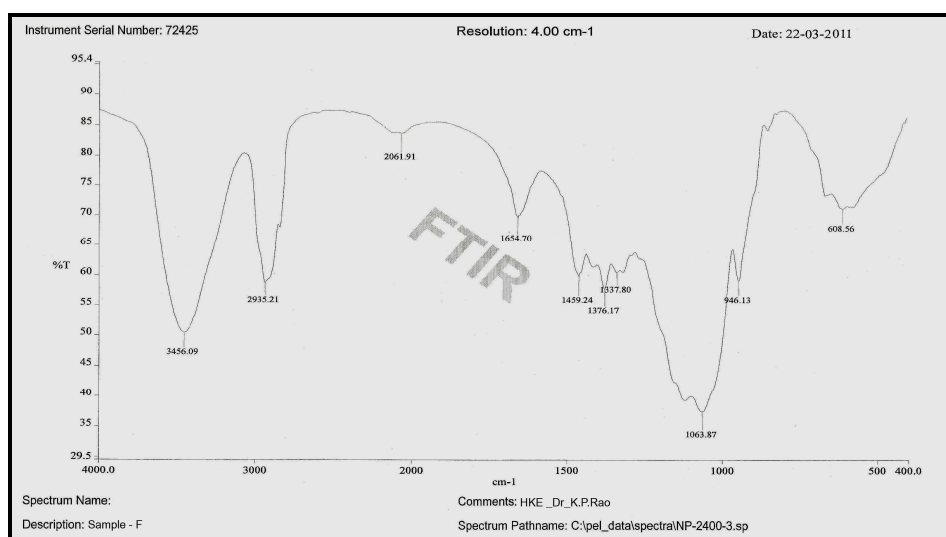


Figure 2: IR Spectra of Ketoconazole Dermasticks (KL-I)

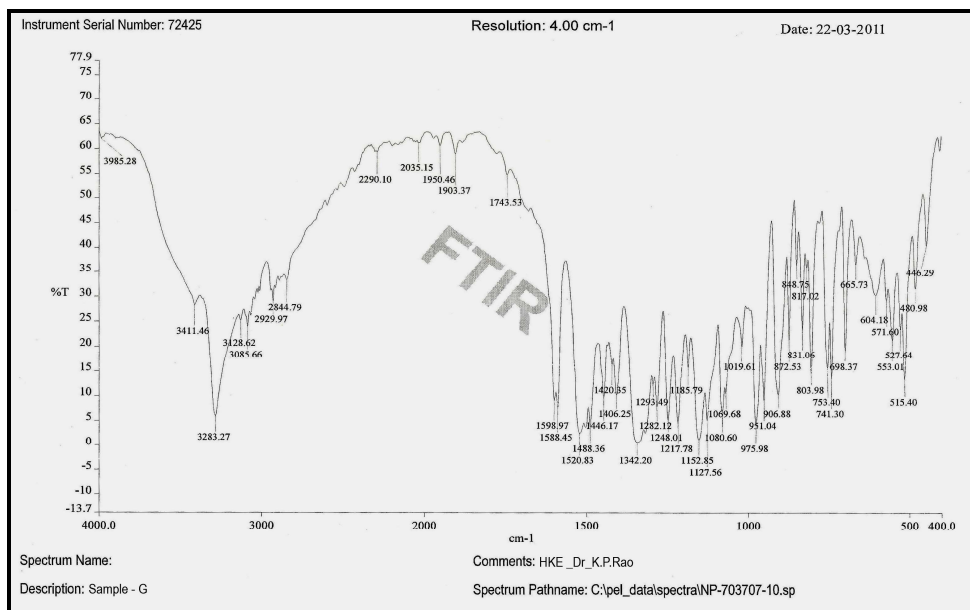
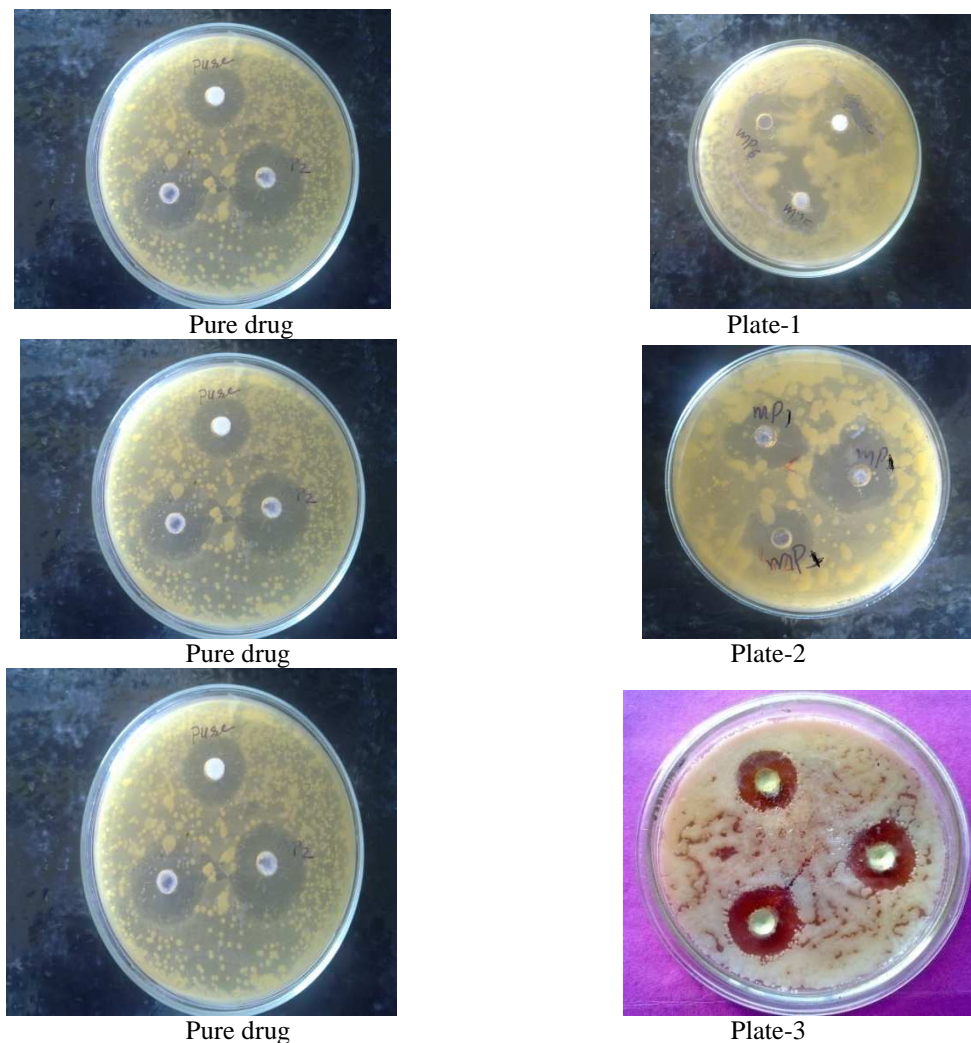


Figure 3: Comparative zone of inhibition of drug as pure and in formulation (kl-i)



Formulation code	Statistical zone of inhibition (mm) after 36 hrs			Mean±S.D
	Zone 1	Zone 2	Zone 3	
Pure Drug	23	24	25	23.66±0.57
KL1(plate 1)	19	22	20	20.33±1.52
KL1(plate 2)	20	21	22	21.00±1.00
KL1(plate 3)	20	21	23	21.33±1.53

Table 4: Skin irritation test data of prepared dermastick base in rabbits, guinea pigs and healthy human volunteers

Formulation code	Sex	Before Application			After 24 hrs.of application			After 48 hrs.of application			After 72 hrs.of application		
		I	R	E	I	R	E	I	R	E	I	R	E
KL-I (Rabbits)	Male-I	x	x	x	x	x	x	x	x	x	x	x	x
	Male-II	x	x	x	x	x	x	x	x	x	x	x	x
	Female	x	x	x	x	x	x	x	x	x	x	x	x
KL-I (Guinea Pigs)	Male-I	x	x	x	x	x	x	x	x	x	x	x	x
	Male-II	x	x	x	x	x	x	x	x	x	x	x	x
	Female	x	x	x	x	x	x	x	x	x	x	x	x
KL-I (Healthy human volunteer)	Male-I	x	x	x	x	x	x	x	x	x	x	x	x
	Male-II	x	x	x	x	x	x	x	x	x	x	x	x
	Female	x	x	x	x	x	x	x	x	x	x	x	x

I-Skin irritation, R-Redness, E-Erythema