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DESIGN OF MICONAZOLE DERMA STICKS FOR THE TREATMENT OF SKIN INFECTIONS

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ABSTRACT

Chromomycosis is known as chromoblastomycosis or verrucous 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. In the present study Miconazole a anti bacterial and anti fungal activity has been selected as model drug.. 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 6.4 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 Miconazole are convenient, equally effective, without any contamination chances on application and free from skin irritation.

KEYWORDS: Miconazole, medicated sticks, Dermal disorders.

INTRODUCTION

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.[1-2] An advantage of this drug delivery system includes patient compliance; convenience and comfort ness for efficient treatment include application without fingertip, immediate onset of action, reduced dosage regimen and economy. Miconazole[3,5] that has anti bacterial and anti fungal activity commonly used in the treatment of several skin disorders not available in such dosage form.[6-7] Objective of the present work was to develop a NDDS of miconazole prepared by heating and congealing method a convenient model to use by patients.

MATERIALS AND METHODS

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

Preparation of miconazole stick: Medicated dermasticks of miconazole were prepared by heating and congealing according to the formulae (Table 1). Depending upon the weight, thickness and length of non-medicated derma sticks, the formulae was chosen for the incorporation of the drug. Cetyl alcohol[8,9] and white petroleum was melted in a china dish and heated this mixture upto 70^0C. Dissolved sodium lauryl sulfate, propylene glycol in purified water and heat the solution to 70^0C 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 miconazole content was determined by measuring the absorbance at 271.8 nm 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 miconazole 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:[10]** *In vitro* drug diffusion of prepared miconazole 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 miconazole was taken in the cell (donor compartment) , then the cell was immersed in beaker containing 100 ml of drug free pH 6.4 phosphate buffer[11] (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 $37^oC \pm 1°C$ 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 271.8 nm. The volume of sample withdrawn at each interval was replaced with a fresh quantity of diffusion medium. Cumulative percent of miconazole 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±2ºC).

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 37±2ºC 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 37ºC. 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. & 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±2°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 Miconazole were prepared by heating and congealing method using Cetyl 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 three 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 99.13 to 99.14 % (Table 2). Among the formulations, various concentrations of cetyl alcohol (9.95- 14.75% w/w) was employed as stiffening agent. The *in vitro* drug diffusion was carried out for all the formulations i.e. MS1, MS2 and MS3 in pH 6.4-phosphate buffer over a period of 160 minutes (Table 3). The data reveals that overall, formulation MS1 showed the maximum 53.58% 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 (Fig1,2,3). Antimicrobial studies revealed that the drug in formulation show equal zone of inhibition like pure drug (Table 4). The preclinical studies in animals and healthy human volunteer revealed that the prepared formulations will be safe to use for topical applications (Table 5,6,7).

Table No. 1: Composition of Miconazole Derma Sticks.

Ingredients (mg/stick)	Formulation code		
	MS1	MS2	MS3
Miconazole	10	10	10
Cetyl alcohol	10	12.5	15
White petrolatum	15	15	15
White bees wax	12	14	16
Sodium lauryl sulphate	1.00	1.00	1.00
Propylene glycol	13.00	13.00	13.00
Purified water QS	100.00	100.00	100.00

Table No. 2: Evaluation of Medicated Derma Sticks.

Formulation code	Medicated stick			Drug content (%) miconazole*
	Weight* (gm)	Thickness* (mm)	Length* (cm	
	Mean ± SD	Mean ± SD	Mean ± SD	
MS – 1	4.31 ± 0.08	6.48 ± 0.04	3.98 ± 0.02	99.13
MS – 2	4.26 ± 0.03	6.46 ± 0.02	3.98 ± 0.03	99.11
MS – 3	4.14 ± 0.08	6.49 ± 0.05	3.98 ± 0.02	99.14

* Each reading is an average of three determinations

Table No. 3: *In-Vitro* Drug Release of Miconazole Derma Sticks In Ph 7.4 Phosphate Buffer.

Sl. No.	Time (min)	%Cumulative Drug released*		
		MS 1	MS 2	MS 3
1	00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
2	20	5.12 ± 0.62	4.99 ± 0.53	4.47 ± 0.57
3.	40	16.12 ± 0.56	17.58 ± 0.42	19.98 ± 0.63
4.	60	23.69 ± 0.55	21.97 ± 0.66	25.00 ± 0.57
5.	80	32.78 ± 0.56	29.71 ± 0.43	29.22± 0.55
6.	100	37.23 ± 0.94	34.89 ± 0.80	38.75 ± 0.59
7.	120	39.36 ± 0.40	37.48 ± 0.75	42.24 ± 0.74
8.	140	46.03 ± 0.38	44.89 ± 0.48	46.79 ± 0.48
9.	160	53.58 ± 0.42	50.55 ± 0.69	49.91 ± 0.68

* Each reading is an average of three determinations

* One gm of sample contains 10 mg of drug

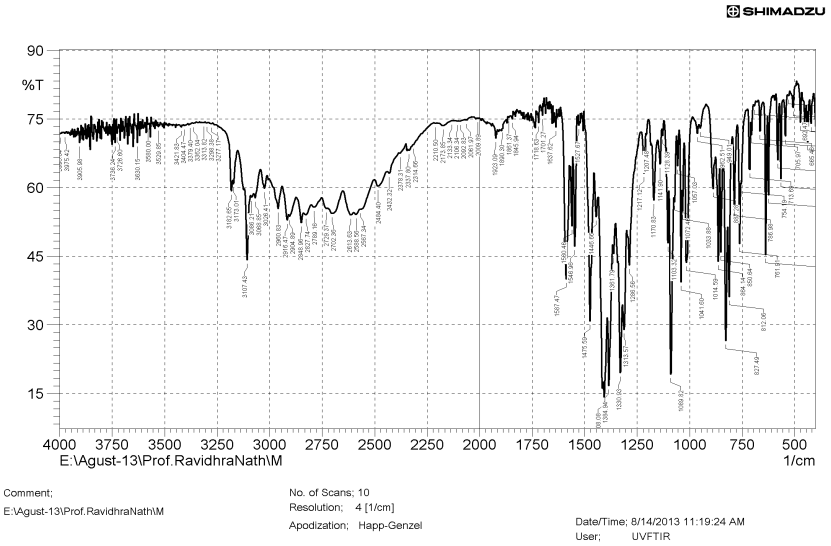


Figure 1: IR Spectra of miconazole (Pure Drug).

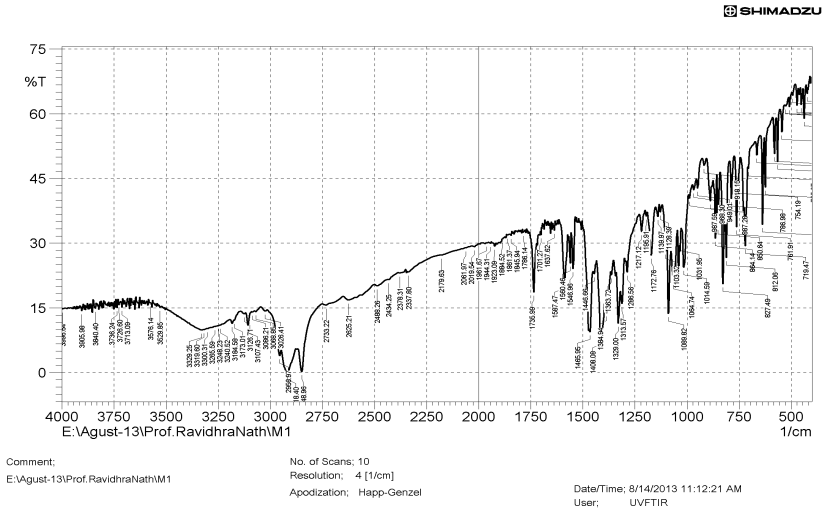


Figure 2: IR Spectra of miconazole Dermastick(MS-I).

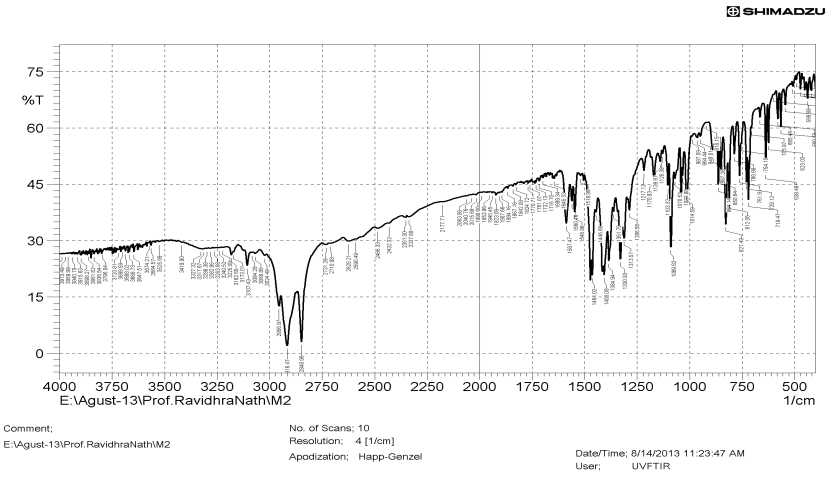


Figure-3: IR Spectra of miconazole Dermastick (MS-II)

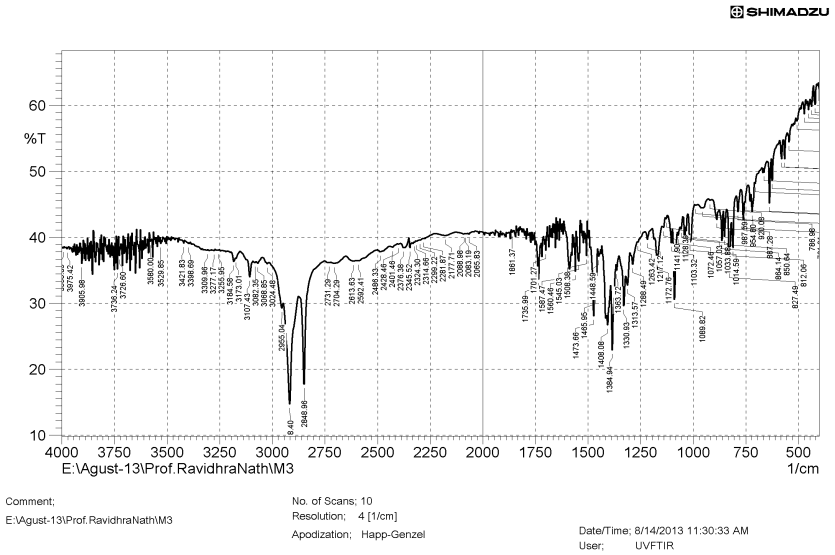


Figure-4: IR Spectra of miconazole Dermastick (MS-III).

PHOTOGRAPHS OF ANTIMICROBIAL STUDIES SHOWING THE COMPARATIVE ZONE OF INHIBITION OF DRUG AS PURE AND IN FORMULATION (MS -I)

Pure drug

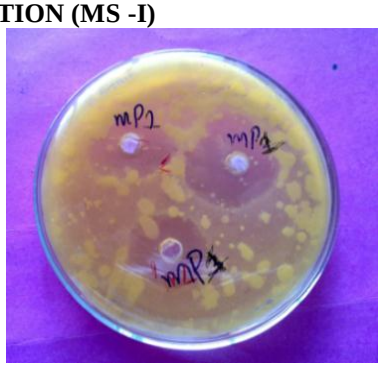
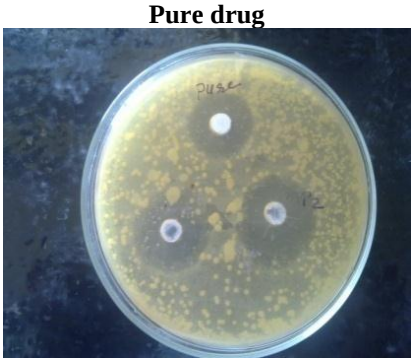


Plate- 1



Pure drug

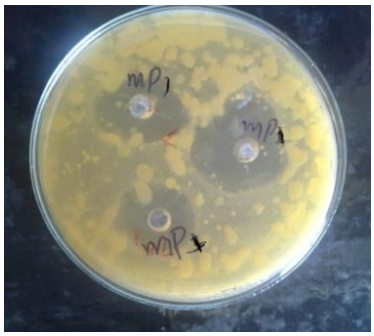
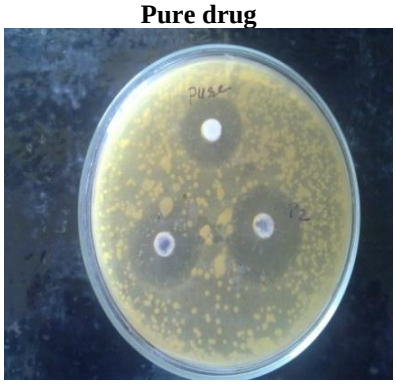


Plate- 2



Pure drug

Plate-3

Formulation code	Statistical zone of inhibition (mm) after 36 hrs			Mean±S.D
	Zone 1	Zone 2	Zone 3	
Pure Drug	23	25	24	24.00 ± 0.57
MS-1 (plate 1)	19	22	20	20.33±1.52
MS-1 (plate 2)	20	21	22	21.00±1.00
MS-1 (plate 3)	20	21	23	21.33±1.53

Table No. 4: Antimicrobial Studies Showing The Comparative Zone of Inhibition of Drug As Pure and In Formulations.

Formulation Code	Statistical Zone inhibition (mm) after 36 hrs			Mean± S.D
	Zone 1	Zone 2	Zone 3	
Pure Drug (Plate 1)	23	25	24	24.00±1.00
Pure Drug (Plate 2)	20	21	21	20.66±0.57
Pure Drug (Plate 3)	24	26	25	25.00±1.00
MS_1(Plate 1)	20	22	19	20.33±1.52
MS_1 (Plate 2)	23	21	21	21.66±1.15
MS_1 (Plate 3)	22	21	19	20.66±1.52
MS_2 (Plate 1)	19	22	20	20.33±1.52
MS_2 (Plate 2)	20	21	22	21.00±1.00
MS_2(Plate 3)	20	21	23	21.33±1.53
MS_3(Plate 1)	19	22	20	20.33±1.52
MS_3 (Plate 2)	20	21	22	21.00±1.00
MS_3 (Plate 3)	20	21	23	21.33±1.53

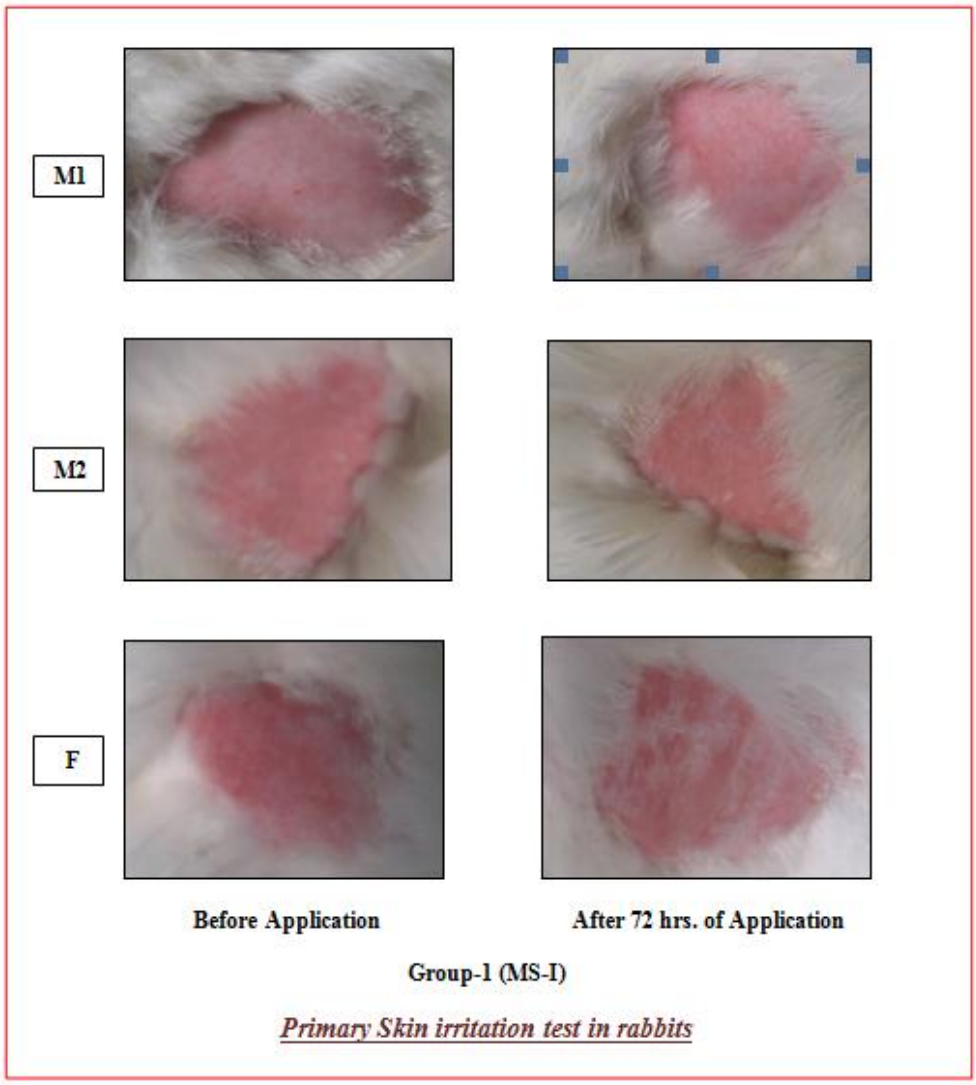


Table no. 5: Skin Irritation Test Data Of Prepared Dermastick Bases In Rabbits.

Formulation code	Rabbits	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
MS-I	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
MS-II	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
MS-III	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

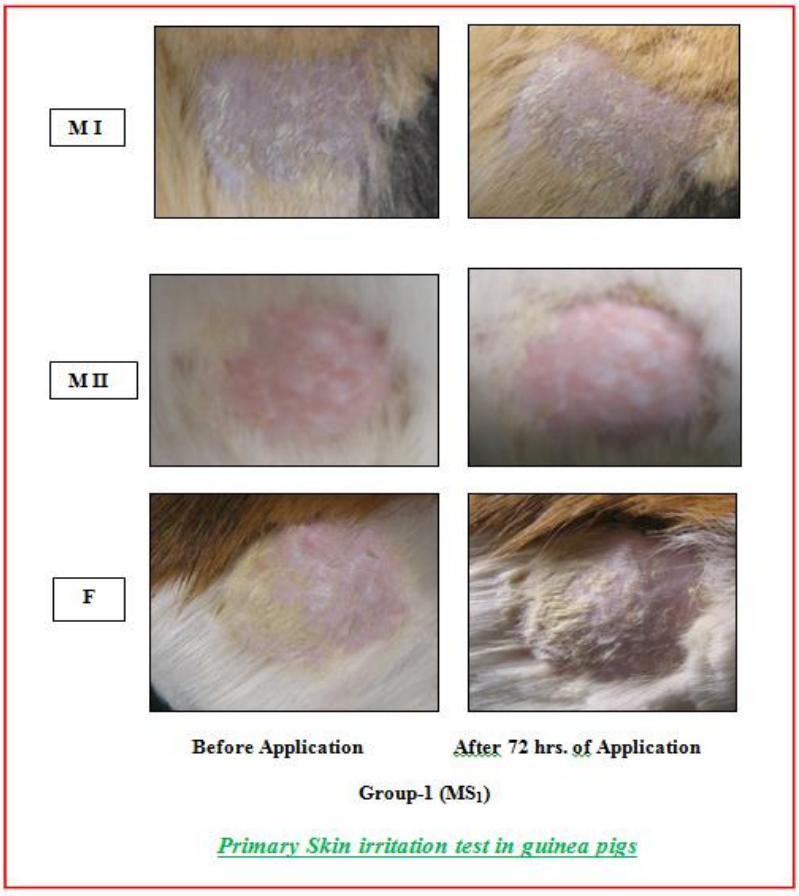


Table No. 6: SKIN IRRITATION TEST DATA OF PREPARED DERMASTICK BASES IN GUINEA PIGS

Formulation code	Guinea pigs	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
MS-I	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
MS-II	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
MS-III	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

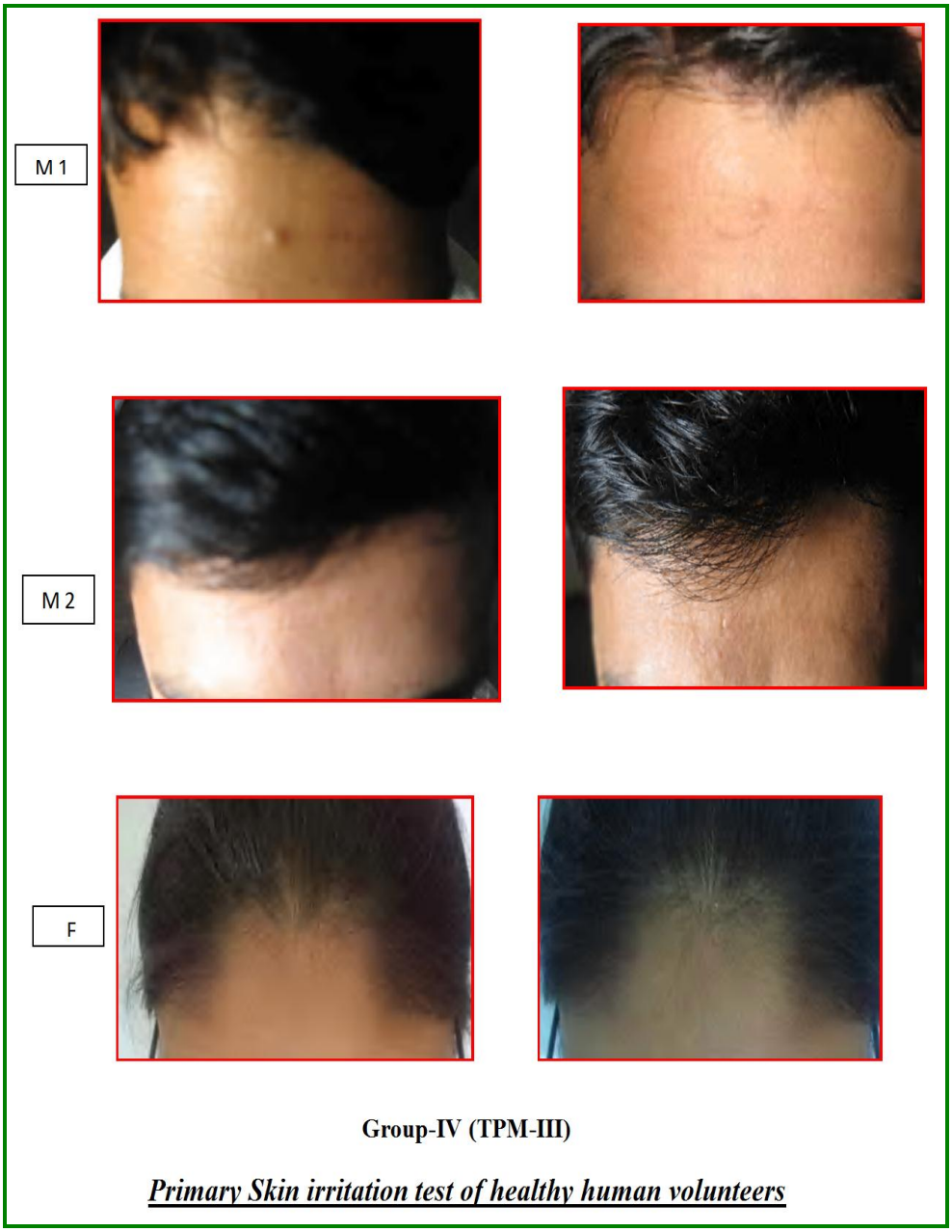


Table No. 7: Skin Irritation Test Data of Prepared Dermastick Bases In Healthy Human Volunteers.

Formulation code	Human Volunteers	Before application			After 24 hrs. of application			After 48 hrs. of application			After 72 hrs. of application		
MS-I	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
MS-II	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
MS-III	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

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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