Academic Sciences

International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 6, Issue 4, 2014

Research Article

FORMULATION OF TRANSDERMAL PATCHES OF MICONAZOLE NITRATE AND ASSESMENT FOR DRUG RELEASE

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Received: 18 July 2014, Revised and Accepted: 08 August 2014

ABSTRACT

Adhesive transdermal patches containing Miconazole Nitrate were prepared as an antifungal therapy. Eudragit RS 100 and Eudragit RL 100 were used in combination as matrix polymers. The patches were assessed for release using a model drug as Miconazole Nitrate by diffusion method. Subsequently, the permeation enhancement effect of DMSO and 2-pyrrolidone was studied. The patches have shown significant controlled release property of the model drug which can be used for a prolonged effect of the drug avoiding the first pass deactivation of Miconazole Nitrate. The patches were also evaluated using various parameters as weight variation, tensile strength, moisture uptake, moisture loss, drug content and other significant parameters. Selected formulations were subjected for their *ex-vivo* studies on rodent skin.

Keywords: Miconazole Nitrate, Eudragit RS 100, Eudragit RL 100, Transdermal patches, Controlled release.

INTRODUCTION

For many diseased states the ideal dosage regimen is that, by which acceptable therapeutic concentration of drug at the site of action is attained immediately and maintained constant for the duration of treatment[1]. Normally this can be achieved and maintained by the repetitive administration of conventional dosage forms such as tablets, capsules, liquids and injectables. However, there are several potential limitations associated with repetitive administration of conventional dosage forms. These limitations are wide in range, fluctuations in the drug concentration in the blood stream, tissues and undesirable toxicity and poor efficacy and unpredictable absorption[2]. Controlled release technology has rapidly emerged over the past decade as a new interdisciplinary science that offers novel approaches to delivery of bioactive agents. These agents include pharmaceutical, agricultural and veterinary compounds. One of the significant controlled delivery is Transdermal drug delivery. Transdermal drug delivery will provide opportunities for innovative, challenging interesting and worthwhile research for the benefit of patient worldwide[3]. The reason for intending the formulation of transdermal patches was the advantages, it offers; they are convenient, non-invasiveness and less traumatic as compared to intravenous delivery. In addition patches are more suitable as a drug delivery system because, highly potent drugs with short half lives can be administered with good tolerance, reducing the need for frequent administration. The best part of this delivery system is the easy application and can be held in place for desired period of time, thus making it suitable for chronic therapy. Transdermal patches, where the drug diffuses through the skin, offer a much more convenient way to administer a drug while still having the benefit of continuous drug release.

MATERIALS AND METHODS

Materials

The Miconazole Nitrate was obtained from Glen Mark Pharmaceuticals, Nasik; Polyethylene Glycol 400, Eudragit RL 100 and Eudragit RS 100 were procured from Research Laboratories Fine Chemical Industries, Mumbai. Evaluation was done on equipments available in laboratory at SPM's College of Pharmacy, Akluj

Methods

Selection of Polymer composition

The components of the system have a great impact on the release rate of the drug and hence it affects the plasma concentration of the drug. Here drug delivery system is in the form of polymeric film containing specified quantity of drug per square centimeter. Based on their solubilities in different solvents, non-interference in the estimation procedure, rate at which the drug is released, film forming capacity the polymers were selected.

In the present study Eudragit RS 100, Eudragit RL 100 was selected.

Formulation of Medicated Films

Table 1: Formulation of Medicated Films

S. No.	Formulation (RL100:RS100)%w/v	PEG 400 w/w	Solvent
1.	FR* 1 (1:1)	1%	Acetone: Ethanol (4:1)
2.	FR 2 (1.2:0.8)	1%	Acetone: Ethanol (4:1)
3.	FR 3 (1.4:0.6)	1%	Acetone: Ethanol (4:1)
4.	FR 4 (1.6:0.4)	1%	Acetone: Ethanol (4:1)
5.	FR 5 (1.8:0.2)	1%	Acetone: Ethanol (4:1)

*FR: Formulation

Incorporation of drug in Eudragit RL100: Eudragit RS100

2% w/v solution of polymers was prepared with varying ratios of Eudragit RL100 and Eudragit RS 100 using Acetone and Ethanol mixture (4:1) as a solvent. PEG 400 in the concentration of 1% of polymer weight was used as a plasticizer. Eudragit RL 100 and Eudragit RS 100 was added in Acetone and Ethanol mixture and dissolved with the help of mechanical shaker, this solution was kept for 15 min.

The drug was then incorporated in the polymeric solution and the plasticizer PEG 400 was added and mixed slowly. 10 ml of this solution was poured on mercury surface placed in the petriplate. This was then allowed to dry at room temperature for 24 hrs. At the time of drying the petriplate were covered with inverted funnel to avoid excess evaporation, air entrapment and dust contamination. After complete evaporation of solvent at room temperature the films were lifted from petriplate and observed for characteristics such as removal from plate, clarity, flexibility stickiness.

Evaluation

Weight Variation

The patches were subjected to weight variation by individually weighing five randomly selected patches. Such determinations were carried out for each formulation[4].

Measurement of Thickness

Thickness was measured using micrometer screw gauge. Each patch was measured for thickness at five different points to ascertain thickness uniformity in patch[5].

Moisture Absorption Studies

The films were weighed accurately and placed in the desiccator containing 100 ml of saturated solution of aluminum chloride, which maintains 79.50% RH. After 3 days, the films were taken out and weighed. The percent moisture absorption was calculated using the formula[5].

$$\% \text{ Moisture Absorption} = \frac{\text{Final Wt - Initial Wt}}{\text{Initial Wt}} \text{ X } 100$$

Moisture Loss Studies

The films were weighed accurately and placed in the desiccators containing 100 ml of saturated solution of calcium chloride. After 3 days, the films were taken out and weighed. The percent moisture loss was calculated using the formula[5].

$$\% \text{ Moisture loss} = \frac{\text{Initial Wt - Final Wt}}{\text{Final Wt}} \text{ X } 100$$

Water Vapor Transmission Rate (WVTR)

Glass vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven. About 1 g anhydrous calcium chloride was placed in the cells and the respective polymer film was foxed over the brim. The cells were weighed accurately and kept in a closed desiccators containing saturated solution of potassium chloride to maintain a humidity of 84%. The cells were taken out and weighed after three days of storage. The amount of vapor transmitted was found using the formula[5,6].

$$\text{WVTR} = \frac{\text{Final Wt - Initial Wt}}{\text{Time X Area}}$$

Measurement of the tensile strength[6]

The measurement of the Tensile strength, the pure polymer solution was taken and blank patch was prepared by using mercury surface placed in petriplate. After that the prepared film was removed and used for the measurement of the tensile strength.

Tensile Strength: $=m/a \times b(1+L/l)$

Where,

m = mass in gms, a = width of a film. b =thickness of film in cm, L=length of film in cm,

l = elongation of film at break in cm.

Formulation of Medicated Films of Eudragit RL100: Eudragit RS100:

Incorporation of the penetration enhancer

The penetration enhancer's 5% Dimethyl Sulphoxide and 2-pyrolidone was incorporated into different polymeric solution having maximum release and the above procedures were repeated[7,8,9].

The other evaluation parameters for medicated films are

Drug Content

A film of size 3 cm^2 was cut into mass piece and put in a 100 ml of phosphate buffer solution of pH 6.9 with 2% Triton X 100. This was then shaken on a magnetic stirrer for 2 h to get a homogenous solution and filtered. From this solution 1 ml was transferred to volumetric flask and volume was made up to 10 ml and the absorbance was recorded at 245 nm[5].

***In vitro* drug release study**

The cellophane membrane was used for *in vitro* drug release study. The cellophane membrane was mounted between the donor and receptor compartment of KC-diffusion cell. The patch was kept in contact with membrane. The receptor compartment contained phosphate buffer solution of pH 6.9 with 2% Triton X100. The assembly was kept on a magnetic stirrer and stirred at a speed of 200 rpm. The temperature of assembly was kept at 37± 1 °C. After each hour, 1 ml of sample was withdrawn and replaced with same medium up to 12 h.

***In vitro* skin permeation study**

For *in vitro* skin permeation study freshly excised rat skin was used. The surface hairs and subcutaneous fatty tissue was removed using scalpel blade. The skin was mounted between the donor and receptor compartment of KC- diffusion cell. The patch was kept in contact with skin. The receptor compartment contained phosphate buffer solution of pH 6.9 with 2% Triton X 100. The assembly was kept on a magnetic stirrer and stirred at a speed of 200 rpm. The temperature of assembly was kept at 37± 1 °C. After each hour, 1 ml of sample was withdrawn and replaced with same medium up to 12 h.

Skin irritation study

The hairs on the dorsal side of Wistar albino rats were removed by clipping 1 day before this portion of the experiment. The rats were divided into 4 groups (n = 6). Group I served as the control, group II received Placebo (transdermal patch), group III received transdermal patch F12, and group IV received 0.8% v/v aqueous solution of formalin as a standard irritant. A new patch, or new formalin solution, was applied daily for 7 days. Finally, the application sites were observed visually for signs of edema or erythema and scored according to Draize's scoring index[10].

RESULT AND DISCUSSION

Weight Variation

Table 2: Weight Variation of Medicated films of FR 1- FR 5:

S. No.	Formulation	Weight Variation (gms)*	Area(cm^2)
1	FR 1	0.1564 ± 0.020	2
2	FR 2	0.1525 ±0.027	2
3	FR 3	0.1581 ±0.020	2
4	FR 4	0.1575 ±0.027	2
5	FR 5	0.1482±0.036	2

*Represents as mean ± SD (n=3)

Weight of Eudragit RL100: Eudragit RS100 was evaluated as 145.0 mg – 158.0 mg.

Moisture Uptake Studies

Eudragit RS has low swell ability property, this property helps to form minimum pores in the matrix which helps in minimum uptake of the moisture from the environment as well as from the body. From this it helps to evaluate that as there is increase in the concentration of hydrophobic polymer Eudragit RS 100 the moisture uptake was decreased.

Table 3: Moisture Uptake Studies of Medicated films of FR 1- FR 5:

S. No.	Formulation	Moisture Uptake % w/w		
		58%RH	78%RH	98%RH
1	FR 1	1.58	4.75	9.84
2	FR 2	2.42	5.56	11.74
3	FR 3	3.05	7.05	13.26
4	FR 4	3.53	8.13	15.14
5	FR 5	4.60	8.59	16.23

Moisture Loss

As there is increase in the concentration of hydrophobic polymer Eudragit RS 100 the moisture uptake was decreased and due to decreased moisture uptake there is decrease in moisture loss.

Table 4: % Moisture Loss of medicated films of FR 1-FR 5

S. No.	Formulation	Moisture Loss (%)
1	FR 1	1.58
2	FR 2	2.29
3	FR 3	2.65
4	FR 4	3.71
5	FR 5	4.42

Water vapor permeability transmission

The use of hydrophobic polymers in the formulation restricts the increase in water vapor permeability transmission. Eudragit RS 100 has low permeability property; increase in this polymer decreases the water vapor permeability transmission rate.

Table 5: WVPT of medicated films of FR 1-FR 5

S. No.	Formulation	Water Vapor Permeability Transmission (72 hrs) in gm/cm^2
1	FR 1	7.29
2	FR 2	7.40
3	FR 3	8.01
4	FR 4	7.11
5	FR 5	7.72

Tensile strength and percent elongation

The above evaluation for Eudragit RL100: Eudragit RS100 shows that the use of 1% PEG 400 shows adequate tensile strength, good elongation properties showed excellent flexibility and can be easily removed from the rings. So 1% PEG-400 was used as a plasticizer.

Table 6: Tensile strength and percent elongation of medicated films of FR1-FR5

S. No.	Formulation	Tensile Strength (dynes/cm^2)	%Elongation at break
1	FR 1	4.88×10^5	60
2	FR 2	4.90×10^5	55
3	FR 3	4.83×10^5	60
4	FR 4	4.85×10^5	55
5	FR 5	4.99×10^5	55

Drug content

The patches were evaluated for the amount of drug present with respect to the standard calibration curve of Miconazole Nitrate. The obtained result shows that the average content of the drug in the patch was found between 98% to 102%.

Table 7: Drug content of Medicated films of FR 1-FR 5:

S. No.	Formulation	% Drug content
1	FR 1	98.55
2	FR 2	98.6
3	FR 3	102.5
4	FR 4	99.9
5	FR 5	96.5

Comparative *In vitro* release study of FR 1-FR 5 medicated films

For Eudragit RL100: Eudragit RS100 patches, Eudragit RS 100 have low permeability and sustain release ability. This is result of more amounts of non-ionic functionalities. The Eudragit RS 100 does not possess higher amount of cations which resists it to interact with ionic functionalities of drug. Thus in spite of being low permeable the solvent present in the environment permeates slowly in polymer and carries drug with same drug. On the other hand Eudragit RL 100 is highly permeable but contains higher amount of cationic charges over Eudragit RS 100. These cationic charges over Eudragit RL100 undergo ionic interaction with the drug which makes it to adhere with drug molecule. Due to these highly permeable Eudragit RL 100 drug releases in sustain fashion in the solvent.

Table 8: Comparative *In vitro* release study of FR 1 - FR 5 medicated films

Time (min)	%Cumulative Release FR 1*	%Cumulative Release FR 2*	%Cumulative Release FR 3*	%Cumulative Release FR 4*	%Cumulative Release FR 5*
0	0.0	0.0	0.0	0.0.	0.0
30	8.94	21.87	8.32	24.63	24.21
60	21.09	24.21	17.17	33.98	33.11
120	27.55	25.72	26.1	42.35	34.12
180	29.08	29.15	32.17	50.21	57.67
240	33.45	36.95	37.06	55.08	59.28
300	36.39	38.74	45.57	59.51	64.61
360	40.46	42.78	53.74	65.05	70.6
420	42.77	45.73	57.96	70.91	73.27
480	46.34	50.19	62.74	73.13	81.51
540	50.18	51	63.62	77.73	90.8
600	54.7	58.53	68.97	81.45	100.13
660	55.49	63.48	72.09	86.47	108.97
720	63.55	68.03	73.02	90.65	115.68

*Represents as mean (n=3)

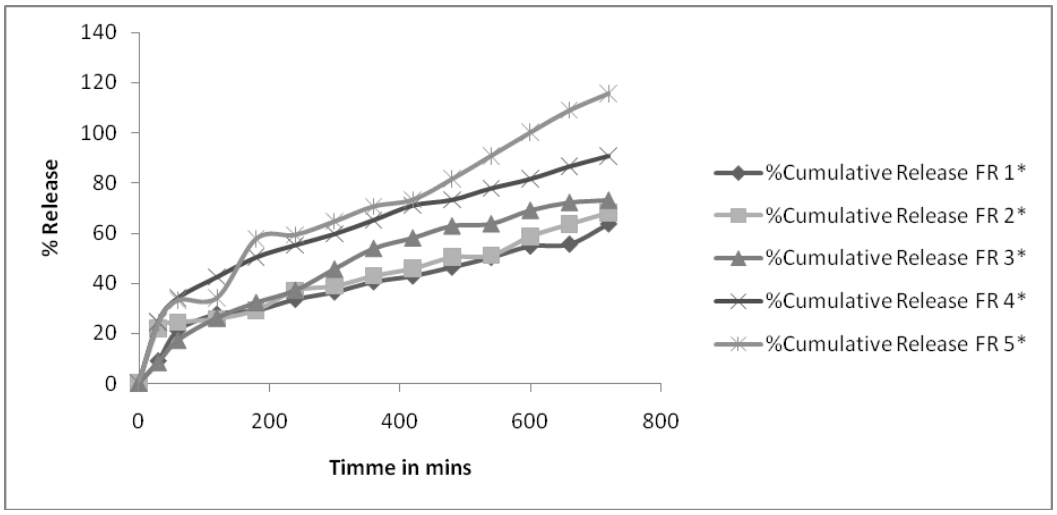

Fig. 1: % Cumulative release of FR 1–FR 5

The release data of Eudragit RL100: Eudragit RS100 of FR1, FR2, FR3, FR4, FR5 formulations showed a % cumulative release of 63.55%, 68.03%, 73.02%, 90.25%, 115.68% respectively. From the comparative study it is concluded that it passes the Matrix model.

Comparative *in vitro* release of FR 4, FR 4 with 2-pyrolidone and FR 4 with DMSO

Table 9: Comparative *in vitro* release of FR 4, FR 4 with 2-pyrolidone and DMSO

Time	%Cumulative Release of FR 4	%Cumulative Release (2-pyrolidone)	%Cumulative Release (DMSO)
0	0.00	0.00	0.00
30	24.63	28.34	37.43
60	33.98	44.68	48.36
120	42.35	50.14	53.93
180	50.21	54.80	61.98
240	55.08	62.11	66.24
300	59.51	65.29	70.57
360	65.05	71.23	72.58
420	70.91	75.37	76.56
480	73.13	78.99	80.56
540	77.73	81.29	84.25
600	81.45	84.98	86.49
660	86.47	88.19	90.79
720	90.65	93.25	96.90

*Represents as mean (n=3)

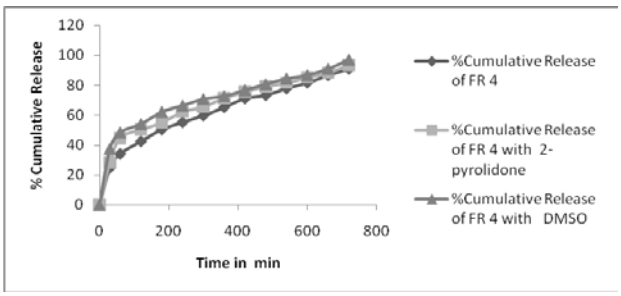

Fig. 2: Comparative % Cumulative Release of FR 4, FR 4 with 2-pyrolidone and DMSO

Skin Irritation Studies

The skin irritation study of the transdermal formulation F12 showed a skin irritation score (erythema and edema) of less than 2 (table. 18). According to Draize et al, compound producing scores of 2 or less are considered negative (no skin irritation). Hence, the developed transdermal formulations were free of skin irritation.

By using Dimethylsulphoxide (DMSO) as a penetration enhancer, DMSO enables low molecular weight substance to penetrate quickly into deeper layers of skin. The sulphoxide does not abolish skin barrier nor does it allow percutaneous absorption of macromolecules. The capability of sulphoxide at moderate concentration to penetrate tissues without damaging them relates to its relatively polar nature, its small compact structure and its capacity to accept H- bonds. This property allows DMSO to associate with water, proteins, carbohydrate, nucleic acid, ionic substance.

Release data of FR 4 using DMSO as a penetration enhancer was increased from 90.65% to 96.90%. By using 2-pyrolidone as a penetration enhancer, 2-pyrolidone helps to establish reservoir of a drug in stratum corneum and in nails. It also produces high degree of epidermal retention. Release data of FR 4 using as a 2-pyrolidone as penetration enhancer was increased from 90.65% to 93.25%.

Table 10: Skin irritation scores following transdermal patch administration

Rat No.	Control		Placebo		FR4		Formalin	
	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema
1	0	0	0	1	2	1	4	**3**
2	0	0	1	0	0	0	2	**2**
3	0	0	1	1	1	1	3	**2**
4	0	0	2	1	1	1	4	**3**
5	0	0	1	0	2	1	3	**2**
6	0	0	1	1	2	2	5	**3**
Avg.	0	0	1±0.25	0.66±0.21	1.33±0.33	1±0.25	3.5±0.42	2.5±0.22

Erythema scale: 0- none; 1- none; 2-well defined; 3- moderate; 4- scar formation.

Edema scale: 0- none; 1- none; 2-well defined; 3- moderate; 4- severe.

**Significant compared with formalin ($P < 0.01$).

CONCLUSION

Penetration enhancers 2-pyrolidone and DMSO were incorporated into the medicated films and their effects on *in vitro* release profile were studied. From the present study it can be concluded that, Miconazole Nitrate can be used as a candidate for transdermal delivery, Eudragit RL 100: Eudragit RS 100 films showed more release, incorporation of 2-pyrolidone and DMSO showed marked increase in drug release, increase in the Eudragit RL 100 concentration in films increases the drug release, increase in hydrophilic polymer concentration in the film, increases drug release.

ACKNOWLEDGEMENT

We are thankful to SPM's College of Pharmacy, Akluj for providing all the facilities for completion of this research work.

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