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FORMULATION AND EVALUATION OF TRANSDERMAL PATCH OF AN ANTIHYPERTENSIVE DRUG

Venna deepthi*, R.S. Thakur, Arshad Bashir Khan

Department of Pharmaceutics, Krupanidhi College of Pharmacy, Sarjapura main road, Carmelaram post, Bangalore-560 035, Karnataka, India.

Corresponding author's Email: vennadeepthireddy@gmail.com Mobile - +918123414314

ABSTRACT

The purpose of this research was to develop a matrix-type transdermal patch containing drug Minoxidil with different ratios of hydrophilic (Hydroxy propyl methyl cellulose) and hydrophobic (Eudragit RL 100) polymeric systems by solvent casting technique by using 15% w/w of Dibutyl phthalate to the polymer weight, incorporated as plasticizer. Formulated transdermal films were physically evaluated with regard to thickness, weight variation, drug content, flatness, tensile strength, folding endurance, percentage moisture loss and percentage moisture uptake. All prepared formulations indicated good physical stability. In-vitro permeation studies of formulations were prepared by using Franz diffusion cells. F4 formulation showed best in vitro skin permeation through rat skin (Sprague dawley). The results followed the release profile of Minoxidil followed Higuchi and peppa's kinetics in different formulation. However, the release profile of the optimized formulation F4 (r^2=0.994 for higuchi) indicated that the permeation of the drug from the patches was governed by a diffusion mechanism. These results indicate that the formulation containing the F4 {HPMC E -15: Eudragit RL 100(4:3)} has shown optimum release in concentration independent manner.

Key words: *Minoxidil, Transdermal patch, Plasticizer, In- vitro permeation study, Skin irritation study, Ex vivo permeation study.*

INTRODUCTION

Transdermal drug delivery of drugs is a novel drug delivery system and this system breaks many barriers in drug therapy like need of assistance, intermediate dosing and uncomfortable administration. Transdermal route of administration is recognized as one of the potential route for local and systemic delivery of drugs, it provides a controlled release of medicament into the systemic circulation [1]

Conventional systems of medication which require multi dose therapy have numerous problems and complications. The design of conventional dosage form, whether a tablet, injection, or a patch, to deliver the right target site becomes complicated if each medication were to be delivered in an optimal and preferred manner to the individual patient. The impetus for the development of novel drug delivery system, apart from therapeutic is cost. Redesigning the modules and means to transport medicine into the body is less demanding and more lucrative task. To address these problems controlled release drug delivery system, novel drug delivery systems approach evolves, which facilitates the drug release into systemic circulation at a predetermined rates [2]

Transdermal systems are ideally suited for diseases that demand chronic treatment. Despite the suitability of TDDS in the treatment of chronic disease like hypertension, the high cost of antihypertensive patches than conventional products made the target patients to think twice. In spite of the high cost of transdermal patches for hypertension

treatment, antihypertensive patches with the established dosage forms reduced the occurrence of hospitalization and diagnostic costs. Further, the possibility of achieving controlled zero order absorption, simple mode of administration and the option of easy withdrawl of dose in case of adverse manifestations make them desirable in antihypertensive therapy. This acceptability factor had encouraged me to take up project in this particular arena.

MATERIALS AND METHODS

Minoxidil was received as a gift sample from Bangalore fine chemicals, Bangalore, India. HPMC E- 15 and Eudragit RL 100 were generous gift from Shreeji chemicals, Mumbai, India. Other materials used in the analytical grade. Distilled water was used throughout the study.

Investigation of Physicochemical Compatibility of Drug and Polymer [3]

The physicochemical compatibility between Minoxidil and polymers used in the films was studied by using fourier transform infrared (FTIR- 8300, Shimadzu Co., Kyoto, Japan) spectroscopy.

The infrared (IR) spectra were recorded using an FTIR by the KBr pellet method and spectra were recorded in the wavelength region between 4000 and 400 cm–1. The spectra obtained for Minoxidil with polymers were compared.

Formulation of drug Free Patches

Polymers of single or in combinations are accurately weighed and dissolve in respective solvent and then castled on a petridish with defined surface area. The films were allowed to dry overnight at room temperature. Then the films are separated and noticed for film formations.

Formulation of drug incorporated Patches [4,5]

Transdermal patches of Minoxidil were prepared by solvent casting method for the formulations shown in table .Solutions of HPMC E- 15 and Eudragit RL 100 were prepared separately in dichloromethane: methanol (1:1) mixture. The two polymeric solutions were mixed to which weighed amount of Minoxidil was added slowly. To the mixture, add 0.1 ml of plasticizer and kept it for stirring for half an hour. The drug- polymer solution was casted on a petridish. The petridish was kept aside for drying at room temperature for 24 hrs. Inverted funnel was placed over the petridish to prevent the current of air. After drying, the patches were peeled from the petridish, wrapped in aluminium foil, and preserved in desiccators for further studies.

Table 1: Formula for Minoxidil Transdermal patch

Ingredients	F1	F2	F3	F4	F5	F6
Minoxidil (mg)	90.4	90.4	90.4	90.4	90.4	90.4
Eudragit RL- 100(mg)	250	350	400	300	200	100
HPMC E-15 (mg)	450	350	300	400	500	600
Dibutylphthalate (ml)	0.5	0.5	0.5	0.5	0.5	0.5
Dichloromethane: Methanol (ml)	25	25	25	25	25	25

EVALUATION OF TRANSDERMAL PATCHES

Physical appearance [6]

The prepared patches were physically examined for colour, clarity and surface texture.

Thickness uniformity [7]

The thickness of patches was measured by using vernier caliper, with a least count of 0.01mm. Thickness was measured at three different points on the film and average readings were taken.

Uniformity of weight [8]

The patch of size 2×2 cm^2 was cut and weight of each patch was taken individually, the average weight of the patch was calculated.

Tensile strength [9,10]

Tensile strength of the patches was determined with Universal Strength Testing Machine (Hounsfield, Slinfold, Horsham, U.K.). The sensitivity of the machine was 1 gram. It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (4×1 cm^2) was fixed between these cell grips and force was gradually applied till the film broke. The tensile strength of the film was taken directly from the dial reading in kg. Tensile strength is expressed as follows;

$$\text{Tensile strength} = \frac{\text{Tensile load at break}}{\text{Cross sectional area}}$$

Folding endurance [11,7,12]

The folding endurance was measured manually for the prepared patches. A strip of patch (2×2 cm^2) was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same without breaking gave the value of folding endurance.

Percentage moisture loss [12,13]

The patches were weighed individually and kept in a desiccators containing calcium chloride. The final weight was noted there was no change in the weight of individual patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight.

$$\%\ Moisture\ Loss = Initial\ Weight - Final\ Weight / Initial\ Weight \times 100$$

Percentage moisture uptake [14]

The patches were weighed accurately and placed in a desiccator where a humidity condition of 80-90% RH was maintained by using saturated solution of potassium chloride. The patches were kept until uniform weight is obtained,

then taken out and weighed. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

$$\% \, Moisture \, Absorption = Final \, Weight - Initial \, Weight / Initial \, Weight \times 100$$

Drug content uniformity[6,15]

The patches were tested for the content uniformity. The patches of size $1cm^2$ was cut and placed in a 100 ml volumetric flask. The contents were stirred using a magnetic bead for 24hrs to dissolve the patches. Subsequent dilutions were made with phosphate buffer (pH 7.4). The absorbance of the solution was measured against the corresponding blank solution at 209nm using UV- visible spectrophotometer. The experiment was repeated three more time to validate the result.

***In vitro* release studies[14,16]**

The fabricated patch were cut into 1 cm^2 and placed on the commercial semi permeable membrane (regenerated cellulose which was permeable to low molecular weight substances) and attached to the diffusion cell such that the cell's drug releasing surface towards the receptor compartment which was filled with phosphate buffer solution of pH 7.4 at 37±1 ^{0}C. The elution medium was stirred magnetically. The aliquots(1ml) was withdrawn at predetermined time intervals and replaced with same volume of phosphate buffer of pH 7.4. The samples were analysed for drug content using UV spectrophotometer at 275nm.

Skin irritation studies

A primary skin irritation test was performed since skin is a vital organ through which drug is transported. Skin irritation studies were performed on healthy rabbits (average weight: 1.5 to 2.25 kg). The dorsal surface (50 cm^2) of the rabbits was cleaned, and the hair was removed by shaving. The skin was cleansed with rectified spirit. The best formulation (F_4) was placed over the skin with the use of adhesive tape and was removed after 24hrrs. The resulting skin reaction was evaluated.

***Ex-vivo* permeation studies**

The excised skin of albino rats is made free of hair by shaving. The skin was cleared using rectified spirit and attached with the selected patch formulation. This is placed between donor and receptor compartment of Franz diffusion cell. Aliquots from receptor compartment is collected and is tested for quantification of drug permeated via the excised skin.

Stability studies

The purpose of stability study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. Optimised formulation was selected on the basis of physicochemical characteristics, *in vitro* drug release of the formulations. The formulation was subjected to accelerated stability studies for 6weeks as per ICH guidelines. The most satisfactory formulation was sealed in an aluminium foil and stored at 30 ± 2 ^{0}C, 65 ± 5% RH and at 40± 2 ^{0}C, 75 ± 5% RH for 6 weeks.

RESULTS AND DISCUSSIONS

In the present work efforts have been made to prepare transdermal patches of minoxidil by using different polymers ratios such as HPMC E -15 and Eudragit RL 100. The study was targeted to reduce the frequency of dose of minoxidil by using different combinations of the above mentioned polymers and the plasticizer used was dibutylphthalate. The prepared formulations were subjected to various physicochemical characteristics such as percentage moisture absorption, percentage moisture loss, drug content, thickness, folding endurance and weight uniformity. The results are shown in table 2. The release characteristic of the formulation was studied in *in vitro* diffusion studies, *ex vivo* study by using rat skin.

Table 2: Physicochemical Evaluation data of minoxidil transdermal patches

Formulation	% Moisture uptake	%Moisture Loss	Thickness(mm)	Weight variation(mg)	Folding endurance	% Drug content
F1	3.156±0.049	7.486±0.185	0.15±0.00	142.36±0.25	177±2.94	83%
F2	2.773±0.110	5.216±0.271	0.173±0.004	144.13±1.79	82±4.89	80.5%
F3	6.606±0.358	6.48±0.284	0.216±0.009	164.6±0.2	72.6±4.02	84.6%
F4	1.54±0.175	9.17±0.258	0.226±0.004	155.5±1.30	123.6±7.54	91.9%
F5	2.84±0.104	6.813±0.750	0.16±0.00	145.2±0.52	89.3±2.86	88.3%
F6	5.08±0.108	4.55±0.227	0.176±0.004	152±0.2	97.6±4.92	90.6%

Physical appearance

The patches were smooth and transparent/translucent in appearance.

Thickness

With the help of Digital calipers, the thickness of patches was measured and the average thickness was noted. The thickness results are given in Table 2. The result indicates that there was no much difference in the thickness within the formulations. The order of the thickness of patches is $F_1<F_5<F_2<F_6<F_3<F_4$.

Weight uniformity

Drug loaded patches (2×2 cm^2) were tested for uniformity of weight and the results of weight uniformity are given Table 2. Lesser S.D. values indicate that the patches a uniform. The order of the weight of patches is $F_1<F_2<F_5<F_6<F_4<F_3$.

Folding endurance: The recorded folding endurance of the patches was shown in Table 2. It depicts all formulations have good film properties. The folding endurance of the patches are in the following order $F_3<F_2<F_5<F_6<F_4<F_1$.

Percentage moisture absorption

The recorded Percentage moisture absorption of the patches was shown in Table 2. The percentage moisture absorption of the prepared patches are in following order $F_4<F_2<F_5<F_1<F_6<F_3$.The results show the moisture absorption of all the patches are within the acceptable limit.

Percentage moisture loss

The recorded Percentage moisture loss of the patches was shown in Table 2. The percentage moisture loss of the prepared patches are in following order $F_6<F_2<F_3<F_5<F_1<F_4$

Drug content uniformity

Drug content of the patch was carried out to ascertain that the drug is uniformly distributed in to the formulation. The results obtained are represented in the table 2. From the results obtained (i.e., lowest S.D. values), it was clear that there was proper distribution of minoxidil in the film formulations. Hence it was concluded that drug was uniformly distributed in all the formulation.

***In vitro* diffusion studies**

The *in-vitro* diffusion studies of patches using cellophane membrane barrier was carried out using modified diffusion cell. The results of *in vitro* diffusion studies are shown in Figure 1

The cumulative percentage of drug release from F1 to F6 formulations was given in the following order $F_4>F_6>F_5>F_3>F_2>F_1$.

From the graph it is evident that drug release is decreased with the increase in concentration of Eudragit RL 100 polymer.

The release kinetics was evaluated by making use of Zero order, First order Higuchi's Diffusion and Korsemeyer-Peppas's equation. The drug release through the transdermal patches of minoxidil follows higuchi and peppas order kinetics with diffusion controlled mechanism.

By fitting in the Korsemeyer- Peppa's equation the release kinetics follows non-fickian kinetics. The range of 'n'value for Korsemeyer –Peppa's equation -1 to 1. If the 'n' values of Korsemeyer-Peppa's equation is below 0.5, which indicates Fickian kinetics. If the 'n' value of Korsemeyer-Peppa's equation is in between 0.5 to 1, this indicates non- Fickian kinetics. Here the patches of minoxidil release kinetics fitted in Korsemeyer-Peppa's equation 'n' values are in between 0.5 to 1, so the release is following non-Fickian diffusion controlled kinetics.

Skin irritation studies

Skin irritation studies confirm that there was no sign of skin reaction (erythema or edema) after application of patch on rat skin and that indicates the prepared transdermal patch is free from significant skin irritation

Ex vivo skin permeation studies

Ex vivo permeation study was carried out for optimized formula F4 in the same manner as the *in vitro* permeation study except that Sprague dawley rat's skin contained stratum corneum excised from the dorsal surface was used instead of dialysis membrane.

When the cumulative amount of drug permeated per square centimeter of patches through rat's skin contained stratum corneum was plotted against time, the permeation profiles of the drug followed Peppas equation.

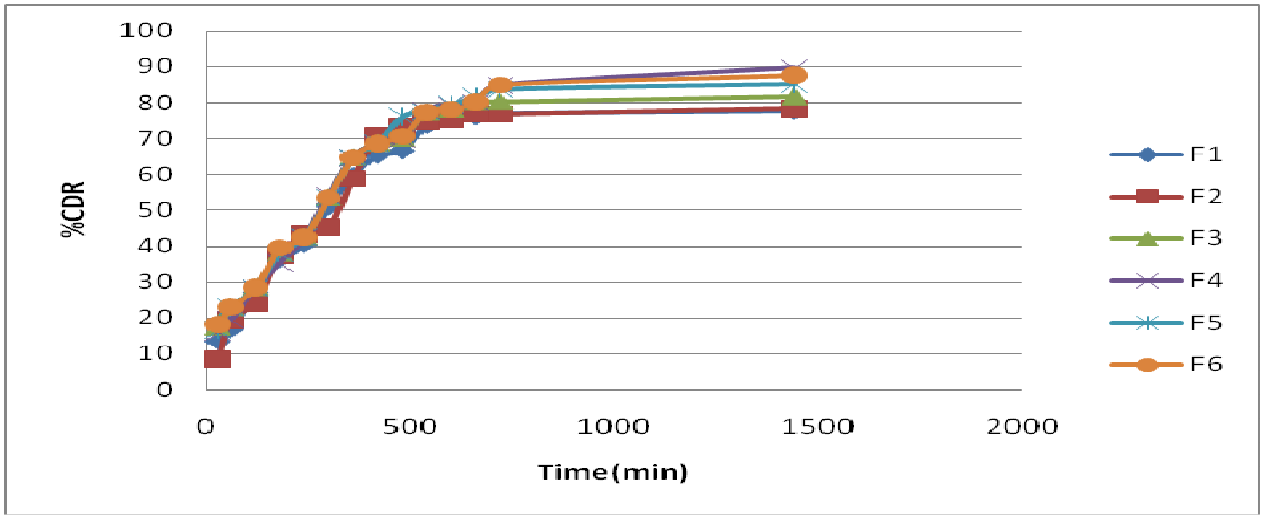

Figure 1: *In- vitro* drug diffusion data of Minoxidil Transdermal patches (F1 to F6) %CDR *vs* Time

Table 3: Regression co-efficient (R^2) values of Minoxidil transdermal patches according to kinetic models

Formulation	Zero order	First order	Higuchi	Peppas	'n' values for Peppas
F1	0.951	0.965	0.984	0.969	0.754
F2	0.937	0.943	0.969	0.987	0.848
F3	0.942	0.942	0.983	0.966	0.635
F4	0.947	0.970	0.984	0.994	0.646
F5	0.945	0.968	0.980	0.962	0.746
F6	0.940	0.969	0.983	0.969	0.646

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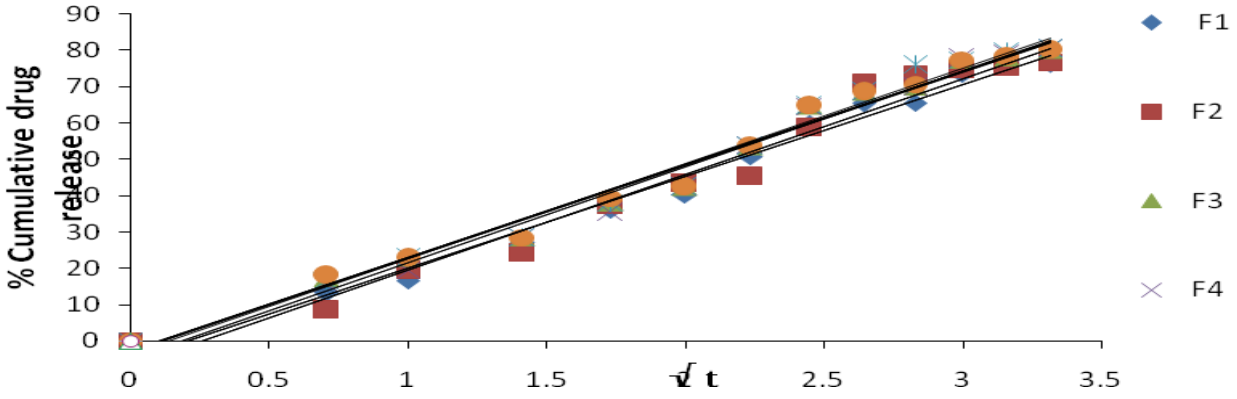

Figure 2: Higuchi drug diffusion data of Minoxidil transdermal patches

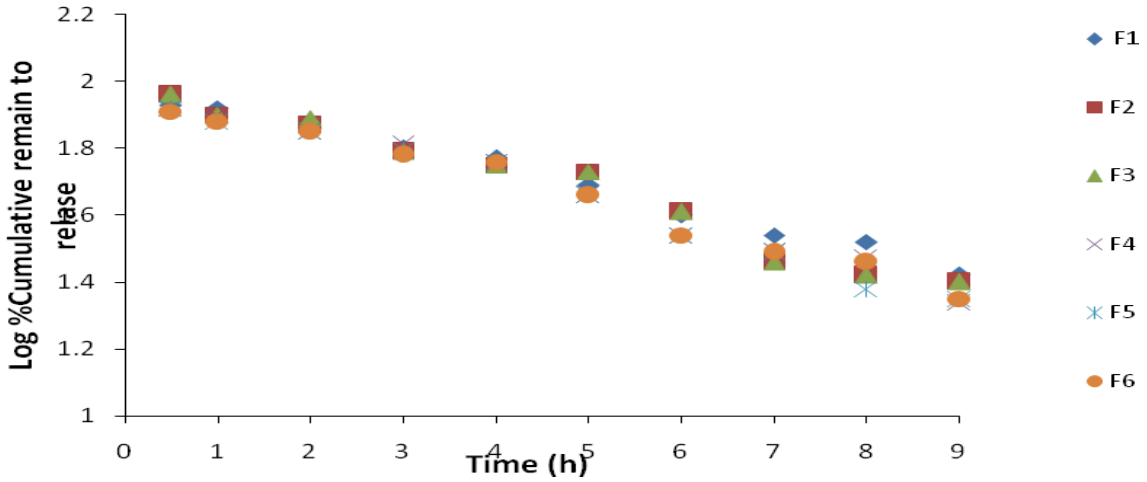

Figure 3: First order drug diffusion data of Minoxidil Transdermal patches

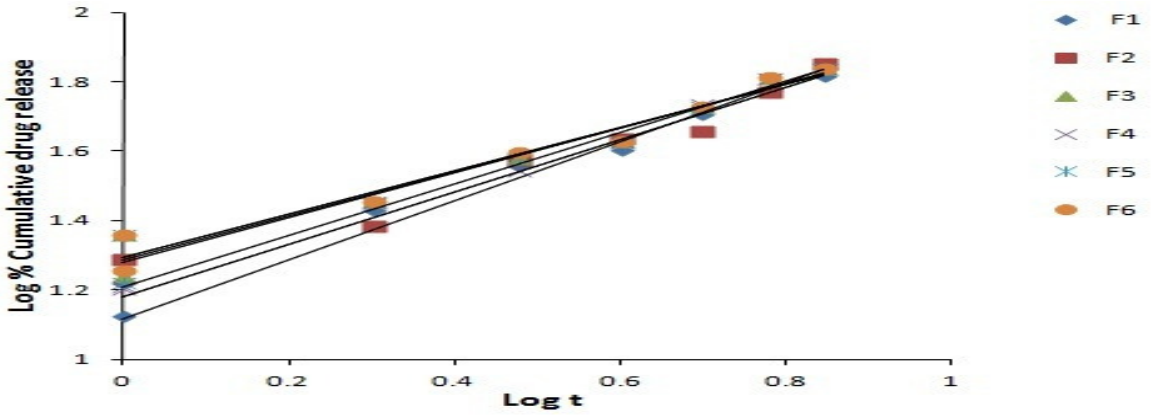

Figure 4: Peppas drug diffusion data of Minoxidil Transdermal patches

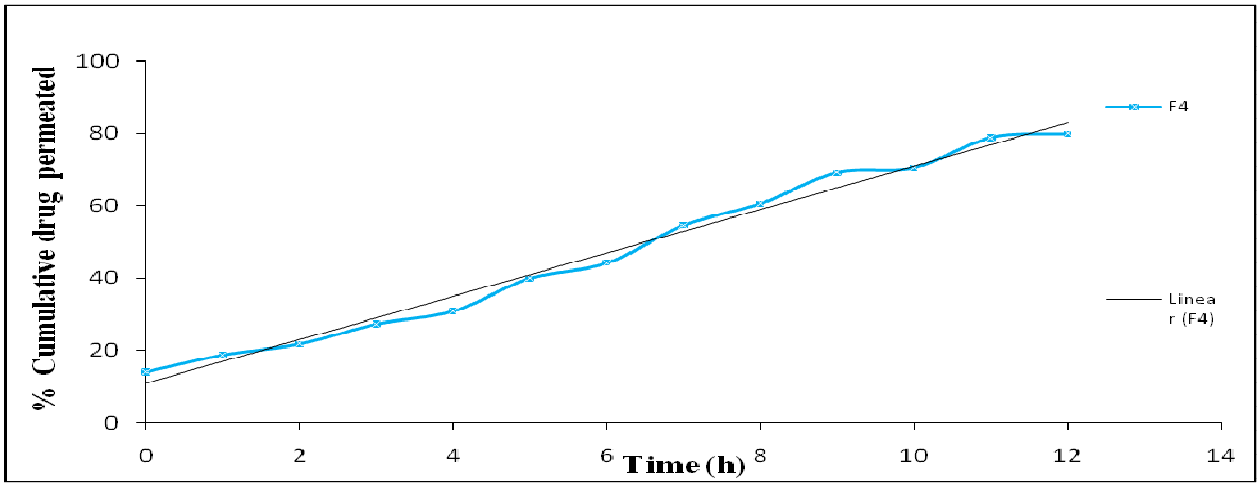

Figure 5: *Ex vivo* drug permeation data of Optimized formula

Skin irritation studies:

Skin irritation studies shows there was no sign of erythema after application of patch on rat skin.

Accelerated Stability studies

Optimized Formulation was selected for accelearted stability studies as per ICH guidelines. The patch was observed for colour, appearance and flexibility for a 6 weeks. There was no change in the physical appearance, folding endurance and drug content.

CONCLUSION

The preformulation studies involving description, solubility, melting point of the drug were found to be comparable with the standard. Based on the all the above preformulation studies that drug was suitable for making the transdermal formulation.

Based on all these factors the transdermal drug delivery system F4 is showing better controlled release upto 24hrs when compared to other formulations.

So it was concluded that the formulation F4 prepared by using HPMC:Eudragit RL 100(4:3 ratio) is the better formulation for control release of drug up to24hrs of time. However the *in vitro* drug release of the best formulation F4 follows Higuchi kinetics and the mechanism of drug diffusion. Results of the present study encouraged that the minoxidil with polymers HPMC and Eudragit RL 100 transdermal patch can be used as controlled drug delivery system and frequency of drug administration can be minimized.

From the above studies, it is clearly indicated that the minoxidil transdermal patches containing HPMC and Eudragit RL 100 in the ratio (4:3) was the best formulation among the prepared patches.

Further detailed investigation and elaborate *in vivo* studies can be carried out and *in vitro- in vivo* correlation can be guarantee the efficiency and bioavailability of the formulation.

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