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Design, Preparation and Characterization of Minoxidil Transdermal Patches

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Abstract

Minoxidil transdermal patches were prepared to sustain the release and improve bioavailability of drug and patient compliance. Different formulations were prepared using various polymers by solvent casting method. The prepared formulations were evaluated for various parameters like thickness, tensile strength, folding endurance, % moisture content, % moisture uptake, % drug content and in vitro drug release. Formulation F2 was selected as optimized formulation which contains HPMC and ethyl cellulose with in vitro drug release of 96.89±0.59% in 12 hr. The release profile of Minoxidil followed Higuchi and peppa's kinetics in different formulation. However, the release profile of the optimized formulation F2 indicated that the release of the drug from the patches was governed by a diffusion mechanism.

Keywords

Minoxidil, polymers, FTIR studies, solvent casting technique, *in* vitro drug release studies.

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1. INTRODUCTION

Transdermal drug delivery system (TDDS) has been an increased interest in the drug administration via the skin for both local therapeutic effects on diseased skin (topical delivery) as well as for systemic delivery of drugs[1]. Transdermal route of administration is recognized as one of the potential routes for local and systemic delivery of drugs, it provides a controlled release of medicament into the systemic circulation[2]. Transdermal drug delivery systems are topically administered medicaments in form of patches that deliver the drug for systemic effects at a predetermined controlled rate. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering various classes of drugs. These devices allow pharmaceuticals to be delivered across the skin barrier [3]. A drug is applied in a relatively high dosage to the inside of a patch, which is worm on the skin for an extended period of time. Through a diffusion process, the drug enters the blood circuation through the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow[4]. The transdermal delivery can also eliminate pulsed entry into the systemic circulation, which might often cause undesirable side effects[5]. Minoxidil (6- (1-Piperidinyl) -2, 4- pyrimidinedi amine 3- oxide) has been widely used as only topical drug for the treatment of androgenic alopecia in men and women [6]. The aim of this work is to develop and characterize minoxidil transdermal patches.

2. MATERIALS AND METHOD

2.1 MATERIALS

Minoxidil was collected as a gift sample from Reddy' laboratories, Hyderabad, natural and synthetic polymers and other excipients were purchased from AR chemicals.

2.2 METHODODOLOGY [7, 8]

Compatibility studies of drug and polymers:

In the preparation of patch, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Pre-formulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Minoxidil and the selected polymers. The pure drug and drug with excipients were scanned separately.

Formulation design

Table 1: Formulation of Minoxidil Transdermal Patches

S. No	Formulation code	Ingredients (mg)						
		Drug (mg)	HPMC	Ethyl cellulose	Xanthan gum	Sodium alginate	DMSO	PEG
1	F1	100	100	900	-	-	1ml	4ml
2	F2	100	900	100	-	-	1ml	4ml
3	F3	100	-	-	100	900	1ml	4ml
4	F4	100	-	-	900	100	1ml	4ml
5	F5	100	-	-	-	1000	1ml	4ml
6	F6	100	-	-	1000	-	1ml	4ml
7	F7	100	1000	-	-	-	1ml	4ml
8	F8	100	-	1000	-	-	1ml	4ml

Preparation of transdermal patches

Solvent casting technique.

Transdermal patches containing Minoxidil were prepared by the solvent casting technique. The drug Minoxidil was dissolved in methanol. Polymers HPMC, Ethyl cellulose, Sodium alginate and xanthan gum are dissolved in suitable solvent and kept under magnetic stirrer. Then add drug solution into polymeric solution. Sufficient care must be taken to prevent the formation of lumps. PEG was used as a plasticizer, DMSO as a permeation enhancer and added to the mixture and mixed well. It was kept aside for 2 hours to exclude any entrapped air and was then transferred into a previously cleaned Petri plate (40cm^2), drying of patches was carried out in vacuum oven at room temperature. Dried patches were packed in aluminum foil and stored in a desiccator for further evaluation.

Evaluation parameters[8, 9, 10]

Physical appearance

All the prepared transdermal films were observed for color, clarity, flexibility, and smoothness.

Folding endurance

Folding endurance of the patches was determined by repeatedly folding at the same place till it broke. The number of times the patch could be folded at the same place without breaking is the folding endurance. This was repeated on all the patches for three times and the mean values plus standard deviation was calculated.

Thickness of the film

The thickness of each film was measured by using screw gauze. The thickness was measured at three different places on each film and the average thickness of the film was taken as the thickness of the film.

Weight uniformity

The prepared patches are to be dried at 60^{0}C for 4hrs before testing. A specified area of 4.52 cm^2 of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Drug content

The transdermal films (4.52 cm^2) were added to conical flask containing 100 ml of phosphate buffer pH 7.4 contain 0.5% SLS. This was then stirred with magnetic bead at 400 rpm for 2 hrs. The contents were filtered, and the filtrate was analyzed spectrophotometrically. Similarly, a blank was prepared from transdermal films without drug.

Moisture absorption studies

The films were weighed accurately and placed in a desiccator containing aluminum chloride to maintain

79.50% RH. After 3 days, the films were taken out and weighed. The percentage of moisture uptake was calculated using the following formula.

$$\text{Perentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture loss studies:

Three films were weighed individually and kept in a desiccator containing calcium chloride at 37^{0}C for 24 hrs. Then the final weight was noted when there was no further change in the weight of the patch. The percentage of moisture loss was calculated using the following formula.

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

***In vitro* release study:**

The drug release was determined using Franz diffusion cell apparatus with thermostatic at 37±0.5 ^{0}C and stirred at a rate of 200 rpm. Sink conditions was maintained throughout the study. The vessel containing 10ml of phosphate buffer pH 7.4 contains 0.5% SLS solution. Aliquots of 1ml of samples were withdrawn at different time intervals and then analyzed using a UV Spectrophotometer.

Percentage of drug release was determined using the following formula.

$$\text{Perentage drug release} = \frac{Da}{Dt} \times 100$$

Where, Dt = Total amount of the drug in the patch

Da = The amount of drug released

Conditions:

Dissolution Medium: Phosphate buffer pH 7.4 containing 0.5% SLS

RPM: 200

Temperature: 37 ± 0.5^{0}C

Time intervals: 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 11 and 12 hours.

Drug release kinetics

To study kinetics data obtained from invitro release were plotted in various kinetic models.

- **Zero-order equation:**

% R = Kt

This model represents an ideal release profile in order to achieve the pharmacological prolonged action.

- **First order equation:**

Log % unreleased = Kt / 2.303

This model is applicable to study hydrolysis kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water soluble drugs in porous matrices.

- **Higuchi equation:**

% R=Kt$^{0.5}$

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drug.

- **Hixson and Crowell equation:**

(% unreleased) $^{1/3}$ = Kt

This expression applies to pharmaceutical dosage forms such as tablets, where the dissolution occurs in planes that are parallel to drug surface if the tablet dimensions diminish proportionality in such a manner that the initial geometrical form keeps constant all the time.

- **Korsmeyer-Peppas equation:**

%R=Kt ^{n}

Stability studies

Optimized medicated films were subjected to short term stability testing. The transdermal films were sealed in aluminum foils and kept in a humidity chamber maintained at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months as per ICH guidelines. Changes in the appearance and drug content of the stored films were investigated after storage at the end of every week.

3. RESULTS AND DISCUSSION

Drug –excipient compatibility studies:

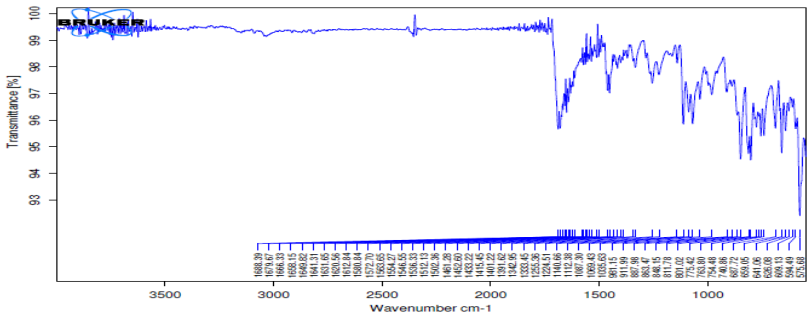

Fig-1: FTIR Studies of Pure drug (Minoxidil)

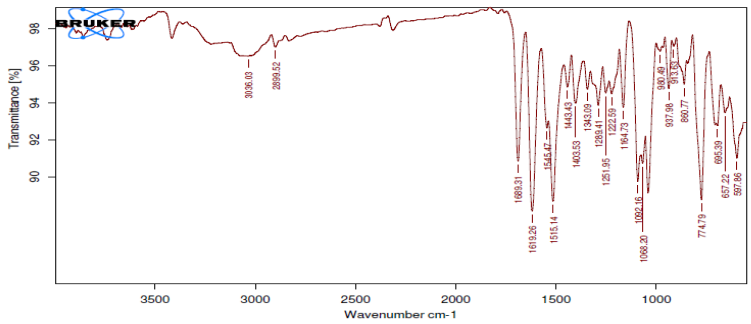

Fig-2: FTIR spectra Optimized formula

The IR spectrum of Minoxidil and Drug Excipients mixture was shown in respectively. In the present study, it has been observed that there is no chemical interaction between drug and the polymers used. From the figures it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers. This further confirms the integrity of pure drug and compatibility of them with excipients.

Evaluation parameters

Physical appearance:

The prepared patches were found to be uniform, smooth, flexible and homogenous.

Folding endurance

The folding endurance numbers of all the Minoxidil patches are 176 – 186. The folding endurance number gives the mechanical property of the patches, high folding endurance number indicate that has high mechanical property. The folding endurance number was increased with increasing the HPMC content. These results indicated that the patches would not break and maintain their integrity with general skin folding when applied.

Thickness of the film

Thickness was changed from batch to batch in individual strips of medicated patch carry uniform thickness, which indicates that total medicated patch carries uniform thickness.

Weight uniformity

The mean weights of all the prepared patches are in the range of 132– 148. The F2 formulation patches showed maximum weight.

Drug content

The drug content analysis of the prepared formulations has shown that the process employed to prepare the patches was capable of giving uniform drug content with minimum batch variability. All the patches were found to have drug content in the range of 93.15±0.29 to 98.68±0.29%. So, the method employed i.e. solvent casting evaporation method is satisfactory for the preparation of Minoxidil transdermal patches.

Table-2: Physicochemical evaluation of Minoxidil patches

Formulation code	Weight (mg)	Thickness (µm)	Folding endurance	Drug content (%)
F1	133±0.26	0.15±0.16	185±0.75	97.26±0.36
F2	137±0.23	0.17±0.19	179±0.69	98.68±0.29
F3	132±0.19	0.14±0.22	183±0.65	94.30±0.32
F4	143±0.16	0.17±0.21	176±0.67	96.55±0.35
F5	148±0.20	0.16±0.20	180±0.70	97.10±0.38
F6	142±0.24	0.14±0.18	186±0.72	95.25±0.31
F7	138±0.26	0.18±0.22	181±0.69	93.15±0.29
F8	141±0.22	0.17±0.26	178±0.71	97.55±0.34

Table-3: Physicochemical evaluation of Minoxidil patches

Formulation code	Moisture loss	Moisture Absorption
F1	5.52±0.16	4.86±0.16
F2	6.35±0.23	4.15±0.23
F3	6.26±0.20	3.25±0.20

F4	5.82±0.19	4.35±0.17
F5	5.52±0.21	4.29±0.15
F6	6.35±0.23	3.18±0.23
F7	5.22±0.28	2.19±0.25
F8	6.55±0.25	3.31±0.20

The moisture absorption in the patches ranged from 5.52±0.56 to 6.55±0.24%. The moisture content in the formulations was found to be increased by increase in the concentration of grade of HPMC. The moisture loss in the patches ranged from2.19±0.25 to 4.86±0.16%. The lower moisture content in the formulations helps them to remain stable and become a completely dried and brittle film. Again, low moisture uptake protects the material from microbial contamination and bulkiness. The drug content ranged from to 93.15±0.29 to 98.68±0.29%. All formulations were acceptable with regard to Minoxidil content.

***Invitro* release study**

The drug release characteristics of the formulation were studied in in vitro conditions by using dialysis membrane. The formulation F1–F8 has shown release of about90.35±0.57%96.89±0.59%, 93.68 ± 0.59%, 96.58 ± 0.38%, 94.28 ± 0.49%, 95.27 ± 0.43%, 92.52 ± 0.62%, and 93.55 ± 0.64%, at 12 hrs, respectively.

Table-4: *In vitro* drug release profiles of Minoxidil transdermal patch (F1-F8)

Time (hrs)	% Cumulative drug released							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	13.45±0.62	11.25±0.60	12.72±0.53	14.50±0.54	13.68±0.46	11.25±0.48	12.25±0.60	14.25±0.62
2	25.29±0.56	24.60±0.58	21.28±0.49	20.28±0.57	26.25±0.52	24.40±0.52	21.27±0.56	20.26±0.58
3	33.26±0.29	31.29±0.57	32.52±0.50	32.18±0.52	33.40±0.51	30.28±0.50	31.25±0.45	32.24±0.56
4	42.98±0.48	42.30±0.55	40.29±0.53	42.21±0.50	42.98±0.49	41.28±0.49	44.30±0.48	43.28±0.59
5	48.60±0.51	53.42±0.51	51.18±0.49	50.25±0.51	53.59±0.50	56.35±0.53	51.18±0.53	50.25±0.62
6	56.54±0.40	59.46±0.55	68.25±0.53	59.56±0.54	62.5±0.53	63.28±0.57	63.23±0.51	62.20±0.66
7	65.50±0.52	61.25±0.54	72.28±0.49	63.50±0.49	69.52±0.52	69.28±0.49	68.25±0.49	69.25±0.60
8	71.35±0.51	72.50±0.58	79.26±0.51	75.25±0.56	72.33±0.49	72.50±0.53	73.20±0.53	71.21±0.58
9	76.89±0.49	79.39±0.60	82.96±0.52	81.26±0.51	82.32±0.50	81.25±0.57	79.25±0.58	79.82±0.57
10	82.15±0.36	85.50±0.62	89.65±0.53	89.58±0.56	88.25±0.53	87.27±0.60	83.45±0.53	81.30±0.59
11	88.39±0.55	90.38±0.58	91.25±0.55	90.25±0.49	92.25±0.54	92.15±0.56	89.21±0.61	89.25±0.62
12	90.35±0.57	96.89±0.59	93.68±0.59	96.58±0.38	94.28±0.49	95.27±0.43	92.52±0.62	93.55±0.64

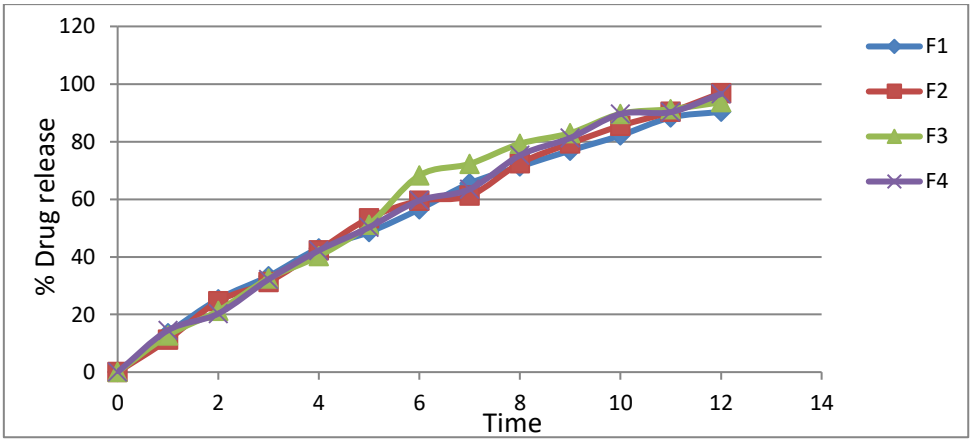

Fig-3: Drug release formulations (F1-F4)

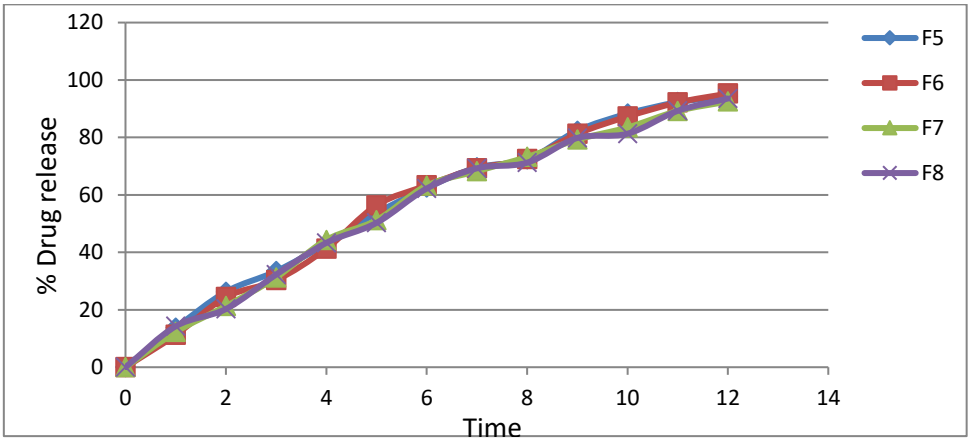

Fig-4: Drug release formulations (F5-F8)

Drug release kinetics

All the five formulation of minoxidil transdermal patches were subjected to invitro release studies and were carried out using Franz diffusion cell apparatus. The dissolution medium consists of 10 ml of Standard buffer pH 7.4.

The results obtaining in vitro release studies were plotted in different model of data treatment as follows:

1. Cumulative percent drug released vs. time (zero order rate kinetics)
2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)
3. Cumulative percent drug released vs. square root of time (Higuchi's
4. Classical Diffusion Equation)
5. Log of cumulative % release Vs log time (Peppas-Exponential Equation)

Zero order kinetics

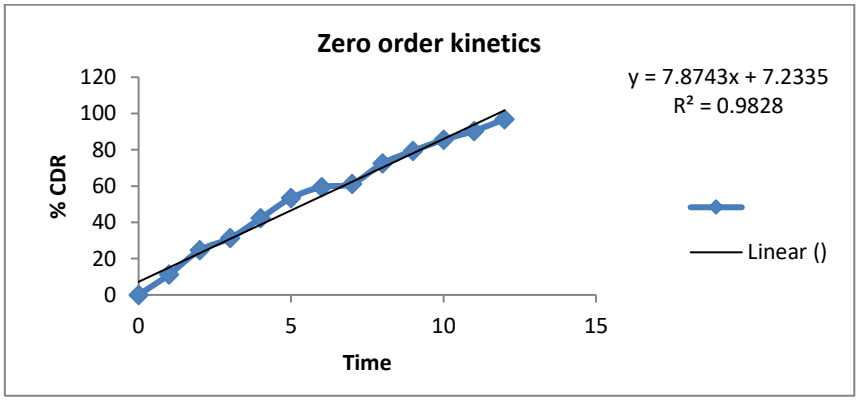

Fig-5: Zero order kinetics

First order kinetics

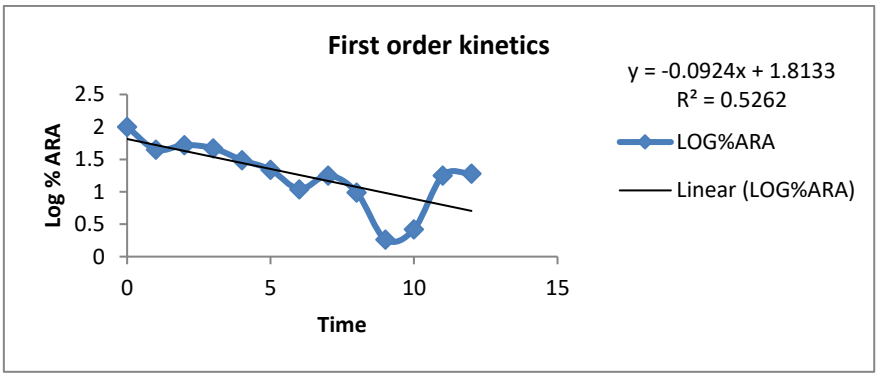

Fig-6: First order kinetics

Higuchi model

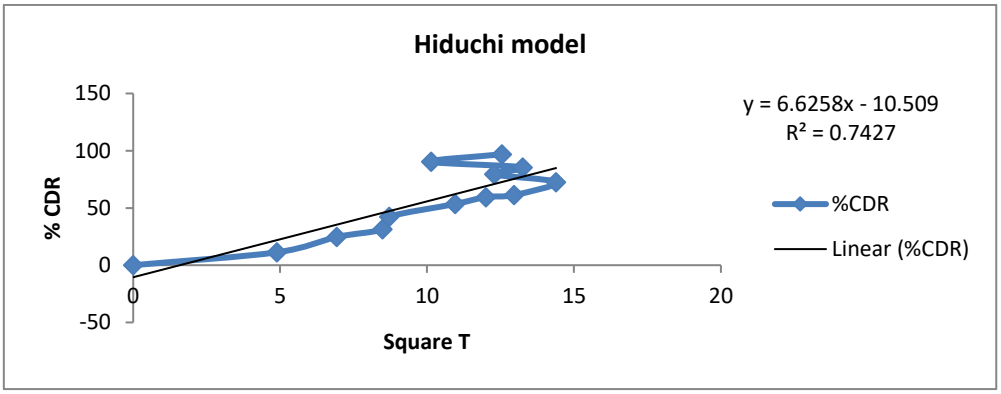

Fig-7: Higuchi model

Korsmeyer-Peppas

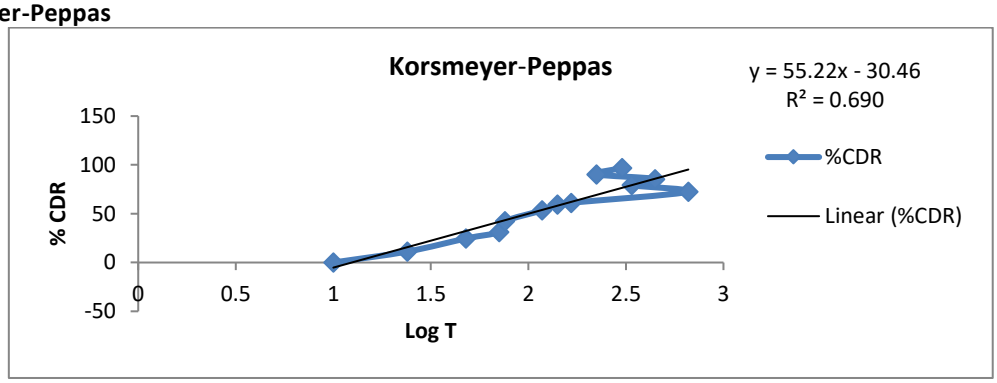

Fig-8: Korsmeyer-Peppas

The values of in vitro release were attempted to fit into various mathematical models. Plots of zero order, first order, Higuchi, Peppas were respectively. Regression values are higher with Zero order release kinetics. Therefore, all the minoxidil transdermal patches follows Zero order release kinetics.

Table-5: Regression equations of Minoxidil transdermal patches

F. no	*In vitro* release in phosphate buffer P^H 7.4 Regression values			
	Zero order	First order	Higuchi Plot	Krossmayerpeppas
F2	0.982	0.526	0.742	0.690

The table indicates that r^2 values are higher for Higuchi's model compared for all the formulation. Hence Minoxidil release from all the transdermal patches followed diffusion rate-controlled mechanism.

Stability studies:

There was no significant change in physical and chemical properties of the patches formulation F-2 after 3 months. Parameters quantified at various time intervals were shown.

F. Code	Parameters	Initial	1st Month	2ndMonth	3rd Month	Limits as per Specifications
F-2	25^{0}C/60%RH % Release	96.89	96.88	96.86	96.82	Not less than 85 %
F-2	30^{0}C/75% RH % Release	96.89	96.87	96.87	96.83	Not less than 85 %
F-2	40^{0}C/75% RH % Release	96.89	96.85	96.86	96.81	Not less than 85%

Table- 6: Results of stability studies of optimized formulation F-2

4. CONCLUSION

Results revealed that prepared patches showed good physical characteristics, no drug-polymer interaction and no skin irritation was observed. The F2 formulation was found to be stable as there was no drastic change in the Physico-chemical properties of the patches, which was also confirmed by FTIR. Thus, conclusion can be made that stable transdermal patches of Minoxidil has been developed. Based upon the *in vitro* dissolution data the F2 formulation was concluded as optimized formulation.

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