



FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF PIOGLITAZONE

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INTRODUCTION

At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks namely poor bioavailability due to first pass metabolism and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be inconvenient.^[1,2]

To overcome these difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise (i.e., site specific), spatial and temporal placement within the body thereby reducing both the size and number of doses. New drug delivery systems are also essential for the delivery of novel, genetically engineered pharmaceuticals (i.e., peptides, proteins) to their site of action, without incurring significant immunogenicity or biological inactivation. Apart from these advantages the pharmaceutical companies recognize the possibility of re-patenting successful drugs by applying the concepts and techniques of controlled drug delivery system in bringing new drugs to the market. One of the methods most often utilized has been transdermal delivery i.e., transport of therapeutic substances through the skin for systemic effect.^[3-7]

The present study was designed to develop a suitable matrix type transdermal drug delivery systems of Pioglitazone using different polymers HPMC E15, Eudragit L100 and to compare the drug release through physical method and chemical method.

Advantages^[8-10]

Delivery via the transdermal route is an interesting option because transdermal route is convenient and safe. The positive features of delivery of drugs across the skin to achieve systemic effects are:

1. Avoidance of first pass metabolism
2. Avoidance of gastro intestinal incompatibility
3. Predictable and extended duration of activity
4. Minimizing undesirable side effects
5. Provides utilization of drugs with short biological half lives
6. Improving physiological and pharmacological response
7. Avoiding the fluctuation in drug levels
8. Avoiding inter and intra patient variations
9. Maintain plasma concentration of potent drugs
10. Termination of therapy is easy at any point of time
11. Greater patient compliance due to elimination of multiple dosing profile
12. Ability to deliver drug more selectively to a specific site

13. Provide suitability for self-administration and enhance therapeutic efficacy

Disadvantages^[11,12]

1. The drugs that require high plasma levels cannot be administered.
2. Not suitable for drugs with high molecular weight.
3. Not suitable for drugs that undergo metabolism during the passage through the skin
4. Not suitable for drugs that produce irritation and contact dermatitis.
5. Variation of absorption rate based on site of application, skin type and patient age.

Anatomy of the skin^[13]

The skin of an average adult human body covers a surface of approximately 2 m² and receives about one third of the blood circulating through the body. It is one of the most readily accessible organs of the human body with a thickness of only a few millimetres (2.97±0.28mm). Its major roles are to regulate body

temperature, protect tissues from infection, prevent fluid loss, cushion internal structures.

The skin can be divided into three distinct layers:

- The epidermis

- The dermis
- The hypodermis

Table 1: Examples of marketed transdermal patches.

Product name	Drug	Manufacturer	Indication
Transderm scop	Scopolamine	Alza / Novartis	Motion sickness
Transderm nitro	Nitroglycerin	Alza / Novartis	Angina pectoris
Vivelle	Estradiol	Noven pharmaceuticals	Post menstrual syndrome
Catapress- TTS	Clonidine	Alza / boehringeringelheim	Hypertension
Duragesic	Fentanyl	Alza / janseenpharmaceutica	Moderate / severe pain
Habitraol	Nicotine	Novartis	Smoking cessation
Androderm	Testosterone	Theratech / glaxosmithkline	Hypogonadism in males
Nuvelle TS	Estrogen / progesterone	Ethical holdings/ schering	Hormone replacement
Butrans	Buprenorphine	Mundi pharma	Opioid analgesic
Emsam	Selegiline	Bristol myer'ssquibb	Parkinson's disease
Daytrana	Methyl phenidate	Noven pharmaceuticals	Attention deficit hyperactivity disorder
Exelon	Rivastigmine	Novartis	Dementia associated with parkinson's disease
Lidoderm	Lidocaine	Grunenthal	Pain associated with post herpetic neuralgia
Tulobuterol	Hokumalin	Abbott japan	Bronchial asthma and chronic obstructive pulmonary disease
Ortho Evra	Norelgestromin/Estradiol	Ortho-Mcneil Pharmaceuticals	Birth control
Prostep	Nicotine	Elan Corp/Lederle Labs	Smoking cessation
Deponit	Nitroglycerin	Schwarz Pharma	Angina pectoris
Combipatch	Estradiol/Norethindrone	NovenInc/Aventis	Hormone replacement therapy

In present work an attempt has made to prepare Matrix type transdermal patches of Pioglitazone using different polymers in different ratios. These patches were evaluated for physico-chemical evaluation and to determine the drug release from these patches. Drug release was compared from the Pioglitazone transdermal patches through physical and chemical methods.

MATERIALS

Pioglitazone was obtained as a gift sample from Aurobindo Pharmaceuticals, HPMC E15 and Eudragit L 100 were obtained from Qualikem fine chemicals Ltd. Chloroform AR and Methanol AR were procured from Merck Ltd, Mumbai. All other chemicals were obtained from Finar chemicals limited, Ahmedabad.

Methodology^[14-19]

Construction of standard calibration curve of Pioglitazone in methanol

The calibration curve is obtained by dissolving 100 mg of Pioglitazone in 100 ml of methanol to give 1000 µg/ml this was stock-I solution. From the above, 1 ml solution was taken and made up to 10 ml with methanol to give 100 µg/ml this was stock- II. From stock-II 1, 2, 3, 4, 5, 6, 7 and 8 ml was taken and made up to 10ml with methanol this gave concentration 10, 20, 30, 40, 50,

60, 70 and 80 µg/ml. Absorbance was measured spectrophotometrically at 280nm against methanol as blank.

Construction of standard calibration curve of pioglitazone in phosphate buffer pH 7.4.

The calibration curve is obtained by dissolving 100 mg of Pioglitazone in 100 ml of pH 7.4 phosphate buffer to give concentration 1000 µg/ml, this was stock-I. from the above, 1ml solution was taken and made up to 10 ml with pH 7.4 phosphate buffer and this was stock- II. From stock-II 1, 2, 3, 4, 5, 6, 7 and 8 ml was taken made up to 10ml with pH 7.4 phosphate buffer this gave concentration 10, 20, 30, 40, 50, 60, 70 and 80 µg/ml. Absorbance was measured spectrophotometrically at 280nm against pH 7.4 phosphate buffer as blank.

Preparation of pioglitazone transdermal films^[20-23]

Matrix type transdermal patches containing Pioglitazone were prepared by solvent evaporation technique, using different ratios of HPMCE 15 and Eudragit L100. The polymers were weighed in requisite ratios and allowed for swelling for about 6h in solvent mixture (1:1 ratio of methanol and chloroform) 15%v/w Polyethylene glycol was incorporated as plasticizer. Then the drug solution was added to the polymeric

solution, casted on to anumbrap triplate of surface area about 66.44cm² allowed for air drying overnight followed by vacuum drying for 8-10hr. The entire sheet was cutting small patches with an area of 4.9cm²i.e. with a diameter of 2.5cm. About 13 patches were obtained from each sheet.

Formulations F1 to F6 composed of HPMC E15 and Eudragit L100 in different ratios. Formulations F7 to F12 were of same composition as the above but penetration enhancer DMSO was incorporated. All formulations carried 15% v/w polyethylene glycol as plasticizer. Composition of Pioglitazone Transdermal Patches is given in Table 2.

Table 2: Composition of pioglitazone transdermal patches.

Formulation code	Drug (mg)	HPMC E15 (mg)	EudragitL100 (mg)	DMSO (ml)
F1	30	600	-	-
F2	30	400	200	-
F3	30	450	150	-
F4	30	500	100	-
F5	30	550	50	-
F6	30	350	250	-
F7	30	600	-	0.03
F8	30	400	200	0.03
F9	30	450	150	0.03
F10	30	500	100	0.03
F11	30	550	50	0.03
F12	30	350	250	0.03

Preformulation study

Preformulation studies are primarily done to investigate the physicochemical properties of drug and to establish its compatibility with other excipients.

FTIR Compatibility Studies

FTIR spectra of pure drug and formulation (with different polymers) were obtained.

Evaluation of pioglitazone transdermal films

The films prepared by general procedure were evaluated for the following properties.

Weight variation

Six films from each batch of an area of 4.90 cm² were weighed individually and the average weight was calculated.

Thickness

The thickness of the film was measured at ten different points on one film using screw gauge. For each formulation three randomly selected films were used and average thickness was recorded.

Folding endurance

Folding endurance of the patch was determined manually by repeatedly folding a small strip of the medicated patch at the same place until broke. The number of times the strip could be folded at the same place without breaking gave the folding endurance number.

Estimation of drug content in polymeric films

The formulated polymeric films were assayed for drug content in each case. Three polymeric films from each formulation were assayed for content of drug.

Films from each formulation were taken, cut into small pieces and was allowed to dissolve in a 100 ml solution containing 50 ml of methanol and 50 ml of chloroform. The solution was diluted suitably and the absorbance of the solution was measured using UV-Visible spectrophotometer at a wavelength of 338 nm against methanol chloroform mixture (1:1) as blank.

Moisture absorption studies

The patches were weighed accurately and placed in the desiccator containing 100ml of saturated solution of Aluminium chloride, which maintains 84 % RH. After 3 days, the patches were taken out and weighed. The percentage moisture absorption was calculated using the following formula

$$\% \text{ Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{initial weight}} \times 100$$

Moisture content determination

The patches were weighed accurately and placed in a desiccator containing calcium chloride at 40°C for 24 h. Then the final weight was noted when there was no further change in the weight of individual patch. The percentage of moisture loss was calculated as difference between initial and final weight with respect to final weight.

$$\% \text{ Moisture absorption} = \frac{\text{Initial weight} - \text{Final weight}}{\text{initial weight}} \times 100$$

Mechanical properties

Mechanical properties of the films were evaluated using a microprocessor based advanced force gauze (UltraTest, Mecmes in, UK) equipped with a 25kg load cell. Filmstrip with dimensions 60x10mm and free from air

bubbles or physical imperfections were held between two clamps position edata distance of 3 cm. During measurement, the top clamp at a rate of 2mm/ spulled the strips to a distance till the film broke. The force and elongation were measured when the film broke. The mechanical properties were calculated according to the following formulae. Measurements were run in four replicates for each formulation.

$$\text{Tensile strength (kg.mm}^{-2}\text{)} = \frac{\text{FForce at break}}{\text{Initial cross sectional area of the sample (mm}^2\text{)}}$$

$$\text{Elongation of break (\%mm}^{-2}\text{)} = \frac{\text{Increase in length (mm)}}{\text{Original length (mm)}} \times \frac{100}{\text{Cross sectional area}}$$

The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters, tensile strength (TS) and elastic modulus (EM) and elongation at break (E/B). Weak polymer is characterized by a low TS, EM and E/B; hard and brittle polymer is defined by a moderate TS, high EM and low E/B; a soft and tough polymer is characterized by a moderate TS, low EM and high E/B; whereas a hard and tough polymer is characterized by a high TS, EM and E/B. Another parameter strain has been use as an indicator of the overall mechanical quality of the film. A high strain value indicates that the ilm is strong and

elastic. Hence it is suggested that a suitable transdermal film should have a relatively high TS, E/B and strain but low EM.

RESULTS AND DISCUSSION

Preformulation study

Preformulation studies are primarily done to investigate the physicochemical properties of drug and to establish its compatibility with other excipients.

FTIR Compatibilty studies

In the FTIR spectra of pure drug and formulation with other ingredients (different polymers) it is observed that the peaks of major functional groups of Pioglitazone, which are present in spectrum of pure drug are observed. It means there are no interactions between drug and other ingredients in a physical mixture and drug is compatible with other ingredients. Preformulation studies such as FTIR are performed for drug and excipient mixtures. In the FTIR spectra of pure drug and formulation with other ingredients (different polymers) it is observed that the peaks of major functional groups of Pioglitazone, which are present in spectrum of pure drug, are observed. It means that there are no interactions between drug and other ingredients in a physical mixture and drug is compatible with other ingredients.^[24,25]

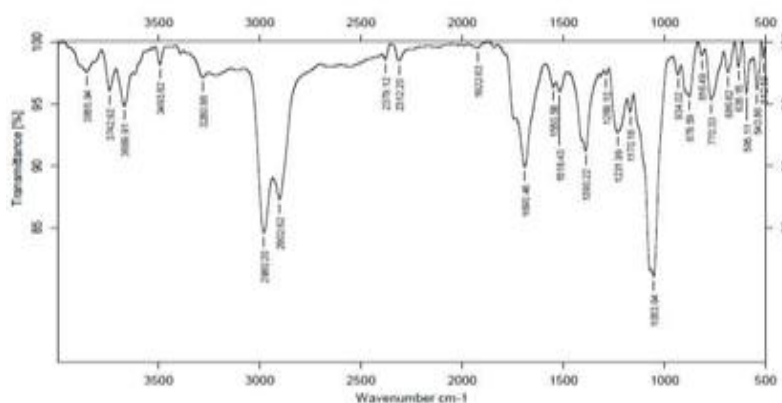


Fig. 1: FTIR spectra of pioglitazone.

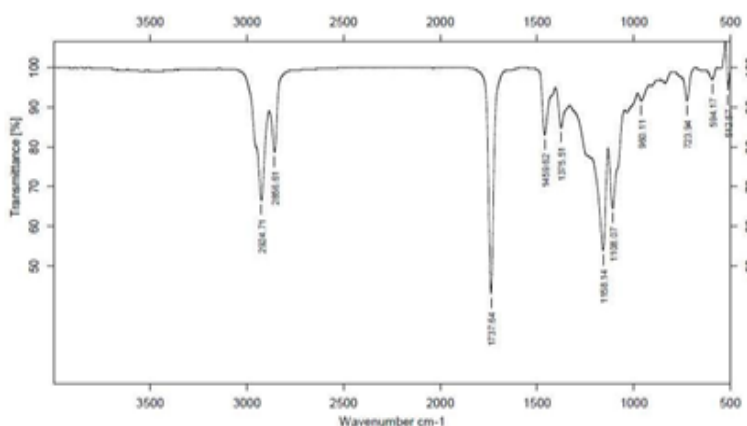


Fig. 2: FTIR spectra of pioglitazone and HPMC E15.

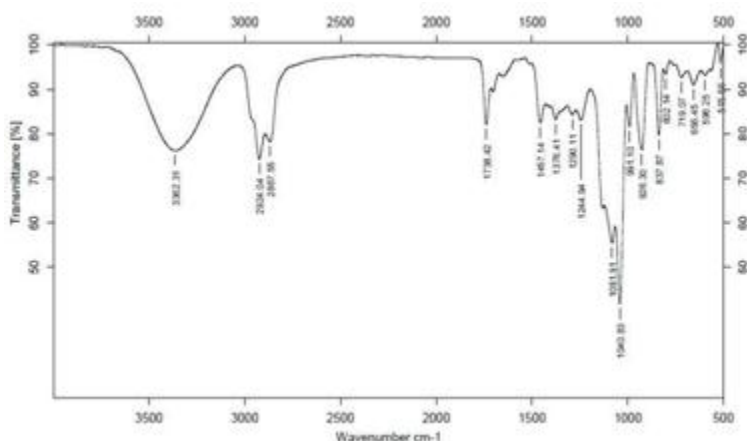


Fig. 3: FTIR spectra of Pioglitazone, HPMC E15 and EL 100.

Construction of standard graph of pioglitazone

The standard graphs of Pioglitazone in methanol and pH 7.4 phosphate buffers were constructed and shown in Fig. 4 and 5. The standard graphs of Pioglitazone in methanol and pH 7.4 buffer have shown good linearity over a concentration range of 10-60 µg/ml with R^2 of

0.9966 and 0.9971 respectively. The standard graph of Pioglitazone in pH 7.4 phosphate buffer has shown good linearity over a concentration range of 10-70 µg/ml with R^2 of 0.9971. These graphs were utilized in estimation of Pioglitazone samples.^[26]

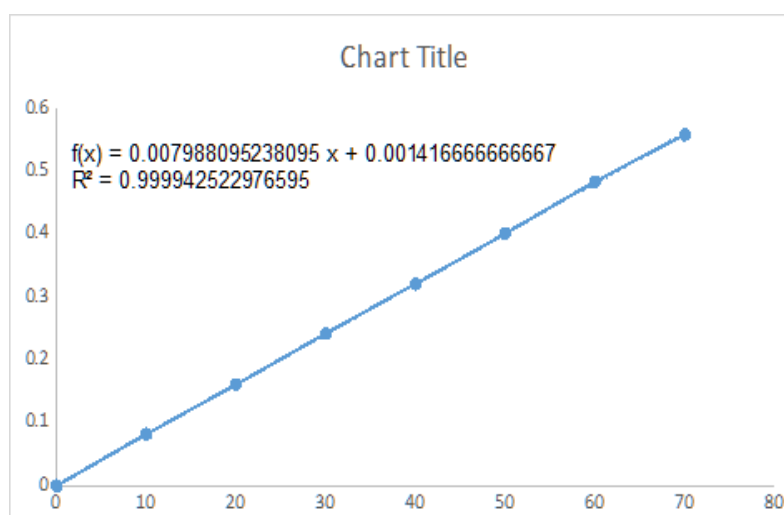


Fig. 4: Standard graph of Pioglitazone in methanol.

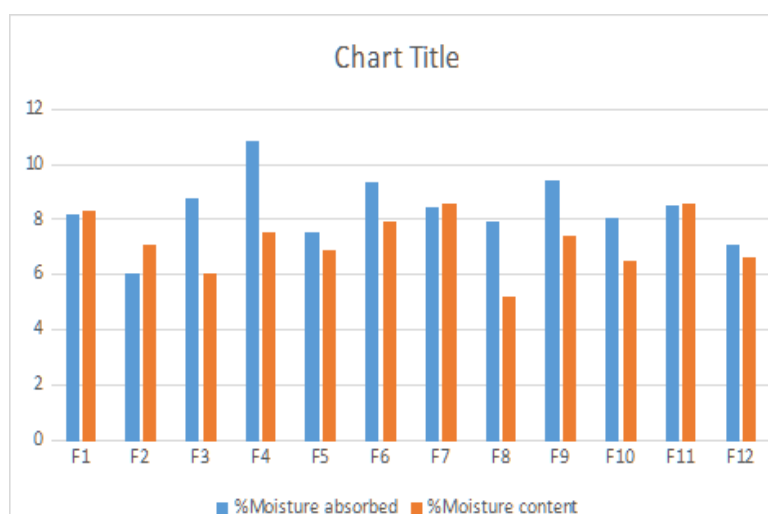


Fig. 5: Standard graph of pioglitazone in pH 7.4 phosphate buffer.

Development of pioglitazone transdermal films^[27-33]

Films were formulated with HPMC E15 and Eudragit L100. Many experiments were performed by varying the concentrations of polymer. The experiment was initiated by taking 0.2 g of polymer and as the polymer concentration increased the patch could accommodate more amount of Pioglitazone. Precipitation of the drug was predominant with 0.2 g of polymer and as the polymer concentration was increased to 0.5 g, the precipitation decreased. No precipitation was observed with 0.6g of the polymer and the films were flexible. Therefore the polymer amount taken was 0.6 g.

In addition, experiments were conducted to know optimal concentration of plasticizer to be used in all kind of films. Plasticizer at concentration of 5%v/w of film former was insufficient to form films. Plasticizer concentration at 5-10% v/w yielded hard and inflexible films. Further, increasing the concentration of plasticizer above 20%v/w resulted in enormous increase in drying time. Therefore films were prepared using 15%v/w of plasticizer and the prepared films were soft and flexible but not brittle. Films were also formulated with penetration enhancer DMSO.

Evaluation of pioglitazone transdermal films**➤ Weight variation test**

The results of weight variation test for various transdermal films were showed in Table 3. Results of weight variation test indicated uniformity in weight of patches, as evidenced by SD values, which were less than 2.0 for all formulations. In formulations F1 to F12 the weight of the patches decreased with decrease in HPMC E15 concentration. weight of the patches ranged from 33.25 ± 0.67 mg for formulation F12 (HPMC E15 and Eudragit L100) to 46.9 ± 1.53 for F1 (HPMC E15). The weight increased with increase in the hydrophilic polymer concentration.

➤ Thickness variation test

In thickness variation test, the thickness was found to be uniform. The thickness increased with increase in HPMC E15 concentration. The SD values were less than 2 for all formulations, an indication of more uniform patches. The results of thickness variation test for various transdermal films were shown in Table 3. The thickness was found to be uniform. The thickness increased with increase in polymer concentration. The SD values were less than 2 for all formulations, an indication of more uniform patches. The thickness range was 0.23 ± 1.54 mm for F6 to 0.30 ± 0.67 mm for F7.

➤ Folding endurance number

The folding endurance numbers of HPMC E15 and Eudragit L100 containing patches has in the range of 434 to 562 as shown in Table 3. 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 HPMC E15 concentration. These results indicated that the patches would not break and would maintain their integrity with general skin folding when applied.

The folding endurance numbers of HPMC E15 containing patches has in the range of 562 to 566 and combination of HPMC E15 and Eudragit L100 containing patches has in the range of 435 to 563. The folding endurance number gives the mechanical property of the patches, high folding endurance number indicate that has mechanical property. The folding endurance number was increased with increasing polymer content. These results indicated that the patches would not break and would maintain their integrity with general skin folding when applied.

➤ Moisture Absorption and Moisture content

The results of moisture content and moisture absorption studies were shown in Table 4. The moisture content in the patches was ranged from 5.22 to 8.59%. The moisture absorption in the formulations is ranged from 6.06 to 10.83%. The results revealed that the moisture absorption and moisture content was found to increase with increasing the concentration of hydrophilic polymer (HPMC E15). The small moisture content in the formulations help them to remain stable and from being a completely dried and brittle film. The results revealed that the moisture absorption and moisture content was found to increase with increasing the concentration of hydrophilic polymer (HPMC E15). The small moisture content in the formulations help them to remain stable and from being a completely dried and brittle film.

➤ Estimation of drug content in polymeric films

Good uniformity in drug content was observed in all transdermal patches as evidenced by low SD values. The drug content is ranged from 2.55 to 3.42 mg per 4.90 cm^2 . The results of drug content for various transdermal films were shown in Table 4. Good uniformity in drug content was observed in all transdermal patches as evidenced by low SD values. The drug content is ranged from 2.73 ± 0.55 mg in formulation F6 (HPMC E15 & Eudragit L100) to 3.42 ± 1.55 mg in formulation F7 (HPMC E15). The drug content was maximum in the formulation containing more amount of hydrophilic polymer.

Table 3: Weight variation, Thickness and Folding endurance of Pioglitazone patches.

Formulation	Weight variation (mg)	Thickness (mm)	Folding endurance
F1	46.9±1.53	0.34±0.79	451.55±0.53
F2	33.76±0.97	0.42±1.27	502.69±1.38
F3	38.26±0.59	0.45±0.95	522.24±0.75
F4	42.41±1.26	0.28±0.83	434.11±0.93
F5	45.75±0.78	0.35±0.56	517.18±0.88
F6	32.37±0.49	0.23±1.54	494.67±0.64
F7	47.55±0.55	0.30±0.67	562.47±1.29
F8	35.45±1.12	0.43±0.98	444.75±1.02
F9	39.62±1.43	0.45±1.38	528.04±0.74
F10	40.78±0.89	0.44±1.26	519.73±0.62
F11	43.51±0.95	0.36±0.58	553.68±1.14
F12	33.25±0.67	0.31±0.63	507.45±1.09

Table 4: Drug content, % Moisture absorbed, %Moisture content of Pioglitazone transdermal patches.

Formulation	Drug content (mg)	%Moisture absorbed	%Moisture Content
F1	3.35±0.96	8.22±1.58	8.34±0.96
F2	2.83±1.29	6.06±1.82	7.07±0.85
F3	3.05±0.84	8.77±0.95	6.04±1.17
F4	3.26±1.18	10.83±1.46	7.55±1.32
F5	3.29±1.04	7.55±0.93	6.87±1.95
F6	2.73±0.55	9.34±1.25	7.96±0.77
F7	3.42±1.37	8.43±1.03	8.59±0.94
F8	2.99±0.92	7.94±0.89	5.22±0.55
F9	3.16±0.75	9.39±0.64	7.40±0.79
F10	3.32±1.55	8.09±0.59	6.54±0.82
F11	3.38±1.27	8.50±1.19	8.60±0.93
F12	2.76±0.86	7.10±1.53	6.66±1.87

➤ Mechanical properties

The results of mechanical properties (tensile strength, elongation at break, elastic modulus and strain) were

shown in **Table 5**. These observations indicate that the optimized formulations were found to be strong and flexible but not brittle.

Table 5: Mechanical properties of optimized formulations.

Formulation code	Tensile strength(kg/m ²)	Elongation at break (%mm ⁻²)
F4	1.25±0.58	18.57±1.42
F9	0.64±0.34	31.65±1.03
F10	1.06±0.78	16.72±0.98

➤ Ex vivo permeation studies through rat abdominal skin and Iontophoresis^[34,35]

The results of *ex vivo* skin permeation of Pioglitazone from patches F1-F 4 were shown in **Fig 6**. The formulations (area of 4.9cm²) containing HPMC E15 and Eudragit L100 (F4 and F10) exhibited the greatest (3082.45±14.2 and 3189.93±6.74µg/cm² respectively) cumulative amounts of drug permeation, which were significantly different compared to the lowest values observed with the formulations containing F5 and F11 (2391.27±6.7 and 2405.94±9.25µg/cm² respectively) in 24h.

As the proportion of HPMC increased in all the formulations increased drug permeation was observed. But with these formulations the required flux was not obtained. The results of *ex vivo* skin permeation of

Pioglitazone from patches prepared with penetration enhancer DMSO (F7 to F12) were shown in **Fig 7 & 8**.

Iontophoresis was performed for 2 h, maintained at a current of 0.5 mA then passive diffusion was carried out for 24h. Formulations F1i to F6i for which, iontophoresis was performed exhibited (F4i 3569.78±9.82 and F3i 3246.84±8.82) greatest cumulative amounts of drug permeation (**Fig 9**). These formulations exhibited the required flux.

The results of drug permeation from transdermal patches of Pioglitazone through the rat abdominal skin confirmed that Pioglitazone was released from the formulation and permeated through the rat skin and hence could possibly permeate through the human skin.

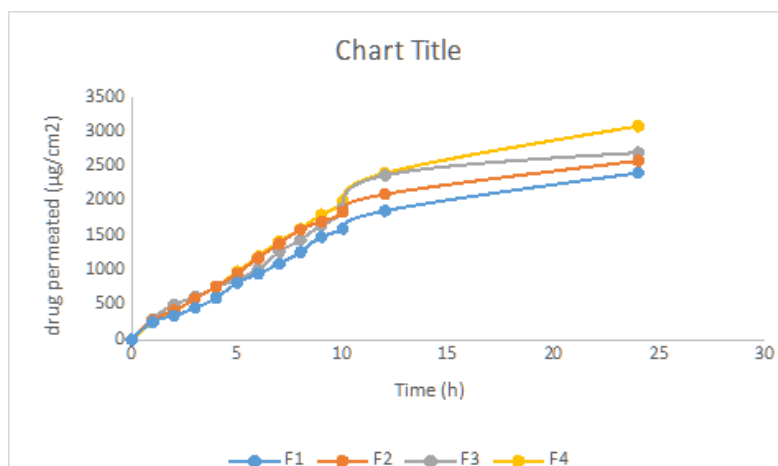


Fig. 6: Permeation of pioglitazone from transdermal patches.

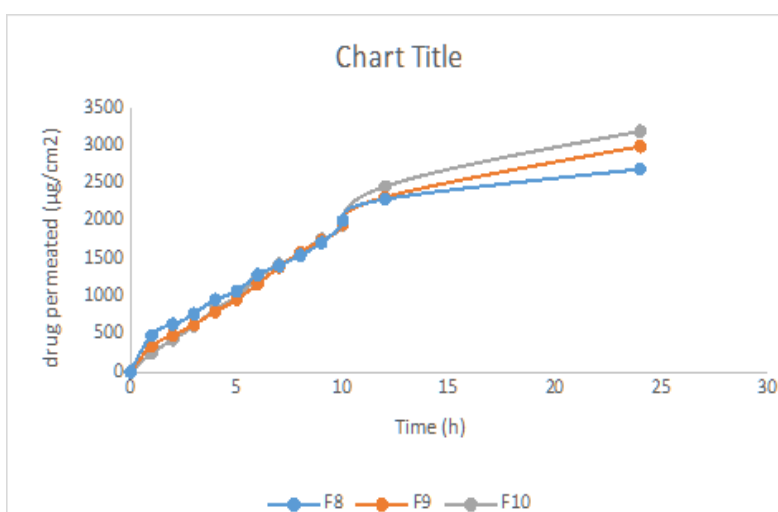


Fig. 7: Permeation of pioglitazone from transdermal patches.

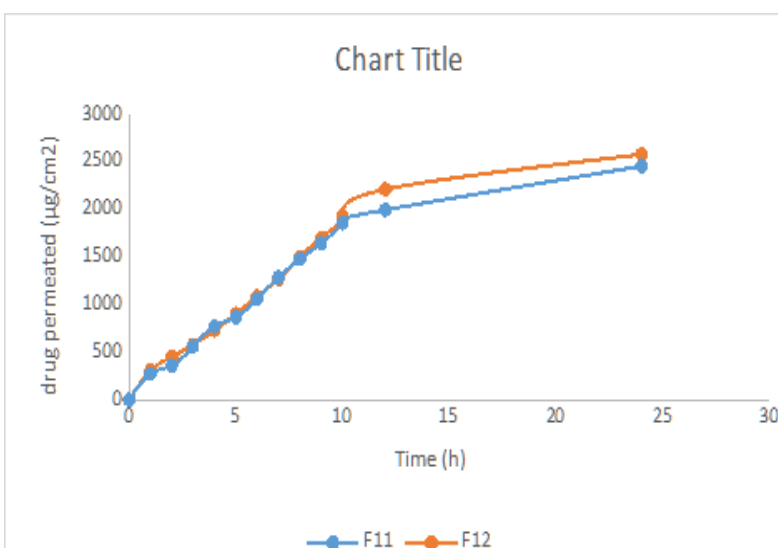


Fig. 8: Permeation of pioglitazone from transdermal patches.

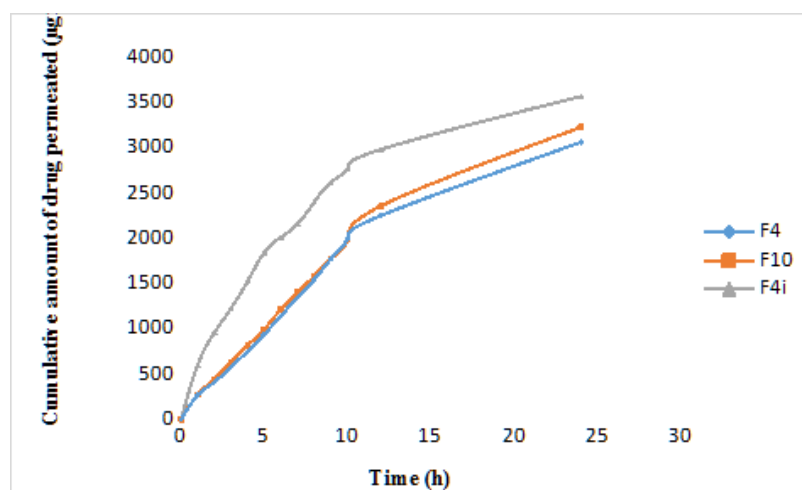


Fig. 9: Permeation of pioglitazone from transdermal patches.

The results of drug permeation from transdermal patches of Pioglitazone through rat abdominal skin confirmed that Pioglitazone was released from the formulation and permeated through the rat skin and hence could possibly permeate through human skin.

CONCLUSION

In the present study, an attempt was made to formulate an anti-hypertensive drug Pioglitazone in the form of transdermal patches using different ratios of HPMC E15 and Eudragit L100. From the results obtained, DMSO enhanced the drug release from the Pioglitazone transdermal patches compared with the normal films. The transdermal patches of Pioglitazone with required flux could be prepared with suitable mechanical properties, further studies are recommended to find their therapeutic utility in humans by further pharmacokinetic studies.

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