Available online on 15.9.2016 at http://ujpr.org
Universal Journal of Pharmaceutical Research
An International Peer Reviewed Journal
Open access to Pharmaceutical research

Volume 1, Issue 1, 2016
Open Access

RESEARCH ARTICLE

DEVELOPMENT AND EVALUATION OF MATRIX TYPE TRANSDERMAL PATCHES OF PIOGLITAZONE HYDROCHLORIDE

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ABSTRACT
Objectives: Pioglitazone hydrochloride is a thiazolidinedione antidiabetic agent; it decreases insulin resistance which leads to decreased hepatic glucose output. It has short half-life, and is extensively metabolized and requires one to two times daily dosing. Present study aims to prepare transdermal patches of Pioglitazone hydrochloride to avoid all these drawbacks associated with it.
Methods: In present study, different transdermal patches of Pioglitazone hydrochloride were prepared using different polymers and evaluated on many parameters. Locally fabricated Franz diffusion cell was used for the *in-vitro* release study. Result revealed that there is a direct relationship with weight of the patch and drug content.
Results: The thickness lies in the range of 0.027 to 0.038mm. Average thickness was almost uniform within same formulation, a small variation in thickness was observed with different formulations. The weight of patches lies in the range of 43.31 to 46.3 mg. The percentage of the drug content lies in the range of 96.87 to 99.28. Content uniformity studies proved that the amount of Pioglitazone hydrochloride in each patch of 2.009 cm^2 was found to be fairly uniform. Percent moisture absorption was found to be in the range of 4.388 to 5.465, largest in formulations of batch code T3 and least in the batch code T2.
Conclusion: The prepared transdermal drug delivery system of Pioglitazone hydrochloride using different polymers such as HPMC, EC, Chitosan and PVP had shown good promising results for all the evaluated parameters. However, for the *in-vitro* drug release and drug content result, formulation T4 was shown to be the optimized formulation, as higher percentage of drug release was obtained.
Keywords: *In-vitro* release, Pioglitazone hydrochloride, stability studies, transdermal patches,

Article Info: Received 1 October 2016; Revised 25 October; Accepted 1 November, Available online 15 November 2016
Cite this article-
Francis DJE. Development and evaluation of matrix type transdermal patches of pioglitazone hydrochloride. Universal Journal of Pharmaceutical Research 2016; 1(1): 17-20.
DOI: ***http://doi.org/10.22270/ujpr.v1i1.R5***
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INTRODUCTION
Transdermal therapeutic systems are defined as 'self contained' discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation[1]. Transdermal route is more convenient as compared to parenteral and oral routes, as it improve patient compliance (no pain) and avoid first pass metabolism respectively. A transdermal patch is a medicated adhesive patch that is placed above the skin to deliver a specific dose of drug through the skin with a predetermined rate of release to reach in to the systemic circulation[2]. Transdermal delivery provides controlled, constant administration of the drug; it allows continuous input of drugs with short biological half-lives and decreases the undesirable side effects, improve physiological and pharmacological response, avoid the fluctuation in drug levels, inter and intra patient variations[3]. Pioglitazone hydrochloride is a thiazolidinedione antidiabetic agent; it decreases insulin resistance in the periphery and in the liver resulting in increased insulin dependent glucose disposal and decreased hepatic glucose output[4]. It improves glucose and, in part, lipid metabolism by increasing insulin sensitivity in insulin-sensitive tissues in diabetic patients. It is a potent and highly selective agonist for peroxisome proliferator activated receptor gamma (PPARγ) that are present in tissues such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism[5]. Pioglitazone hydrochloride was selected as a candidate for the development of transdermal patches as it has a short half-life, is extensively metabolized by hydroxylation and oxidation and requires one to two times daily

dosing. Also unfluctuating plasma concentrations for effective management of blood sugar for long periods in diabetic patients can be maintained by transdermal patches[6].

MATERIALS AND METHODS

Pioglitazone hydrochloride and HPMC K100 was received as gift sample from Afrik Pharmaceuticals Limited, Ethyl cellulose, and Chitosan from Dana Drugs Limited, Nigeria.

Fabrication of the drug free films

A fixed volume of polymer solution with plasticizer was poured onto a glass petri dish. The Petri dish was placed on an even and smooth surface to ensure uniform spreading of the polymer solution. After it, solution was then placed in an oven. An inverted funnel was placed on the petri dish to facilitate the evaporation of the solvent at the controlled rate over the drying periods of 12 hrs at 40°C. The film thus formed was retrieved by cutting along the edges with a sharp razor blade[7].

Fabrication of the Pioglitazone hydrochloride loaded polymeric films

The drug loaded polymeric films were prepared in a similar manner as mentioned above except that a weighed quantity of the 200mg Pioglitazone hydrochloride was added to the polymer solution containing the plasticizer. This solution was poured into a glass petri dish. An inverted funnel was placed on it to control the rate of evaporation. The whole assembly was maintained at 40°C in hot air oven[8]. After 12hrs the film was lifted from the surface of petridish after the cutting the edges with a sharp razor. The film thus formed was neutralized with 2% NaOH and dried.

Table 1: Compositions of the Pioglitazone hydrochloride transdermal patches

Batch	Polymer ratio	Solvent	Plasticizer (20%)
T1	Chitosan :Ethyl cellulose:: 20:80	Acetic acid (1 % w/v)	Castor oil
T2	Chitosan :Ethyl cellulose:: 80:20	Acetic acid (1 % w/v)	Castor oil
T3	HPMC:PVP K30::20:80	Dichloromethane (2% w/v)	Glycerine
T4	HPMC:PVP K30::20:80	Dichloromethane (2% w/v)	Glycerine

Evaluation of transdermal patches

1. Thickness

The thickness of each film was measured at five different places by means of a screw gauge[9].

2. Weight Uniformity

Five patches (area=2.009 cm^2) of each film were weighed accurately and the average weight of the patch was found out[10].

3. Content Uniformity

To determine the amount of Pioglitazone hydrochloride in the patches, the patch of 2.009 cm^2 area was dissolved in 10ml of phosphate buffer solution (pH 7.4) and then after dilution the amount was measured spectrophotometrically at 269 nm[11].

4. Folding Endurance

The folding endurance of the patch was determined by repeatedly folding one patch at the same place up to 290 times, which was considered satisfactory to reveal good patch properties[12]. The number of times the patch could be folded at the same place without breaking gave the value of folding endurance.

5. Percentage moisture loss

The films were weighted accurately and kept in a desiccators containing anhydrous calcium chloride. After 3 days, the films were taken out and weighed[12].

6. Percentage moisture content

The prepared films were weighed individually and kept in a desiccator containing silica at room temperature and the films were weighed again and again until they showed a constant weight. The percentage moisture content was calculated using the following formula[14].

$$\%\ \text{Moisture Content} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} X100$$

7. Percentage moisture absorption

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 percentage moisture absorption was calculated using the formula[15].

$$\%\ \text{Moisture absorption} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Initial Weight}} X100$$

8. Water vapour transmission rate

For this study vials of equal diameter were used as transmission cells. These cells were washed thoroughly an dried in an oven. About 1.0 g of fused calcium chloride was taken in the cells and the polymeric films measuring 2.009cm^2 area were fixed over the brim with the help of an Adhesive[16]. The cells were weighed accurately and initial weight is recorded and then kept in a closed desiccator containing saturated solution of potassium chloride (200ml), containing humidity between 80-90% RH. The cells were taken out and weighed after 1, 2, 3, 4, 5, 6, and 7^{th} day of storage. From increase in the weights the amount of water vapour transmitted and rate at which water vapour transmitted were calculated as shown below.

$$\text{WVTR} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Time x Area}} X100$$

9. Flatness

Longitudinal strips of 1.6 cm in length were cut out from the prepared medicated film and then variation in the lengths due to the non-uniformity in flatness was measured[17]. Flatness was calculated by measuring constriction of strips and a zero percent constriction was considered to be equal to a hundred percent flatness.

$$\text{Constriction}\ (\%) = \frac{l1 - l2}{l2} X100$$

Where, l_1 = final length of each strip, and l_2 = initial length

10. *In-vitro* release studies

A modified Franz-diffusion cell which is also called Keshary–Chein cell was fabricated to study the *in-vitro* release profile. Donor compartment of it was exposed to ambient temperature and a receptor compartment, which was maintained at 37^0C. The patches were stuck to an aluminum foil which was previously cut to have a diameter of 2 cm and a slightly larger patch was fixed using an water-impermeable adhesive[18]. The mouth of the cell was coated with a thin layer of silicone grease to prevent leakage of the receptor fluid 1ml of the receptor fluid was withdrawn at periodic interval for 10 hrs. It was immediately replaced with 1 ml of fresh drug free buffer (pH 7.4) solution to maintain constant volume. The fluid removed, after suitable dilution with phosphate buffer was analyzed spectrophotometrically at 269 nm.

Table 2: Physical Characterization of transdermal patches

Parameter	T1	T2	T3	T4
Physical Appearance	Smooth flexible but wrinkled	Smooth tough	Hard and tough	Smooth tough
Thickness (mm) ± SD	0.028±0.32	0.031±0.25	0.027±0.58	0.038±0.02
Mass uniformity (mg)	46.3±0.35	45.7±0.51	44.3±0.16	43.31±0.23
% Drug content	99.28±0.34	98.66±0.34	97.42±0.12	96.87± 0.42
% Moisture Content	3.21±0.25	2.56 ±0.26	2.78 ±0.25	2.88±0.25
% Moisture absorption	5.342±0.46	4.388±0.82	5.465 ±0.58	4.521±0.33
% Moisture loss	3.763±0.14	3.573±0.15	3.146 ±0.24	3.485±0.32
WVTR (g/cm^2/hrs	$1.521X10^{-4}$± 0.12	1.489 $X10^{-4}$± 0.27	$1.543X10^{4}$±0.08	$1.443X10^{-4}$± 0.12
Folding endurance	> 278	> 285	> 262	> 270
Flatness	100%	100%	100%	100%

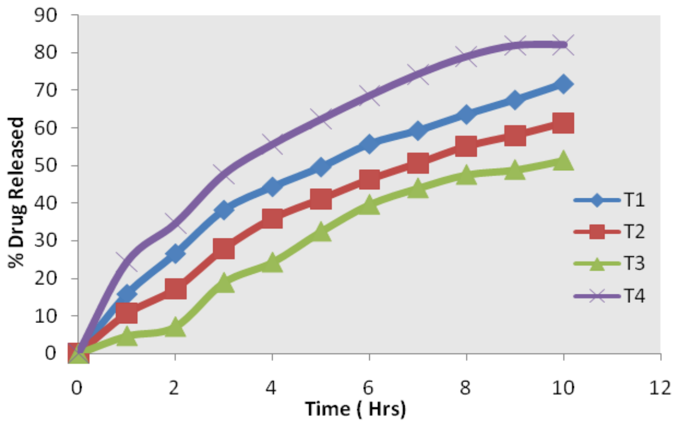

Figure 1: % drug released from Pioglitazone hydrochloride transdermal patches

RESULTS AND DISCUSSION

Four transdermal patches formulations of Pioglitazone hydrochloride were prepared by using different polymers i.e. HPMC, chitosan, PVP K30, EC, in different ratio. Thickness lies in the range of 0.027 to 0.038 mm. Average thickness was almost uniform within same formulation a small variation in thickness was observed with different formulations. The variations in thickness may be due to viscosity of polymer solutions of different formulations. The other reasons may be due to lack of temperature control which have affected the controlled evaporation of solvent from the wet film surface. There is a direct relationship with weight of the patch and drug content. The weight of patches lies in the range of 43.31 to 46.3 mg. The percentage drug content lies in the range of 96.87 to 99.28. Content uniformity studies proved that the amount of Pioglitazone hydrochloride in each patch of 2.009 cm^2 was found to be fairly uniform. Percent moisture absorption was found to be in the range of 4.388 to 5.465, largest in formulations of batch code T3 and least in the batch code T2. Percent moisture content was found to be in the range of 2.56 to 3.21. The folding endurance was measured manually; films were folded 290 times and if the films show any cracks it was taken as the end point. The folding endurance represents the elasticity of the patches. The *in-vitro* permeation of Pioglitazone hydrochloride transdermal patches formulation was studied using locally fabricated Franz diffusion cell.

The cumulative percent drug release after 12 hrs in between 51.4 to 82.11. Largest in batch code T4 and least in formulations of batch code T3. Rapid drug leakage was observed during the initial phase. However, after that a slow release occurred. It was also observed that the drug release generally decreased as the polymer ratio increased. The release of the drug was retarded due to the hydrophobic and insoluble nature of the polymers used. These results indicate hydrophilic nature of polymer PVP K30. Hydrophobic polymer has less affinity for water, this results in decrease in thermodynamic activity of the drug in the film and decreased drug release. The drug release was found to increase on increasing the concentration of hydrophilic polymer in the polymer matrix. This is due to the facts that dissolution of the aqueous soluble fraction of the polymer matrix leads to the formation of gelaneous pores. The formation of such pores leads to a decrease in the mean diffusional path length of the drug molecules to release into the diffusion medium and hence to higher release rates.

CONCLUSION

The prepared transdermal drug delivery system of Pioglitazone hydrochloride using different polymers such as HPMC, EC, Chitosan and PVP had shown good promising result for all the evaluated parameters. Based on the *in-vitro* drug release and drug content, formulation T4 was concluded as an optimized formulation, which shows its higher percentage of drug release.

CONFLICT OF INTEREST

No conflict of interest was associated with this work.

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