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Formulation development and characterization of pioglitazone transdermal drug delivery system

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ABSTRACT

The main objective of the present study was to formulate and evaluate matrix type Pioglitazone transdermal patches and to determine the drug release. Firstly, characterization of the drug was done by performing FTIR compatibility studies and found that there was no interaction between the drug and polymers under study. Formulations (F1 to F6) were prepared using different ratios of HPMC E15 and Eudragit L 100 and penetration enhancer DMSO was incorporated to the above formulations (F7 to F12).These formulations were evaluated for weight variation, thickness variation, folding endurance, %moisture content, %moisture absorption studies, drug content, mechanical properties and *exvivo* permeation studies. In formulations F1 to F12, the drug permeation was maximum for F4 and F10 (ratio 10:2 HPMC E15: Eudragit L100). Among these, formulations F10 is exhibited the required flux.

Keywords: HPMC, Pioglitazone, Transdermal Patch, DMSO.

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]. Continuous intravenous infusion is recognized as a superior mode of drug administration not only to bypass hepatic "first-pass" metabolism, but also to maintain a constant and prolonged drug level in the body [2]. A closely monitored intravenous infusion can provide the advantages of both direct entry of drug into the systemic circulation and control of circulating drug levels [3]. However, such mode of drug administration entails certain risks and, therefore, necessitates hospitalization of the patients and close medical supervision of

administration [4]. 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 with in the body there by reducing both the size and number of doses [5]. New drug delivery system 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 [7]. 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 drug 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 [8].

The present study was designed to develop 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[9]. 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 controlled rate to the systemic circulation [10].

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 medication [11]. A drug is applied in a relatively high dosage to the inside of a patch, which is worn on the skin for an extended period of time[12]. Through a diffusion process, the drug enters the blood stream directly 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 [13].

MATERIALS AND METHODS

Pioglitazone A gift sample from Aurobindo pharmaceuticals, HPMC E15, Eudragit L 100 were purchased from Qualikems fine chemicals Ltd. Polyethylene glycol, Calcium chloride, Aluminium chloride, Potassium dihydrogen phosphate, Sodium hydroxide were purchased from Finar chemicals limited, Ahmadabad.

Pioglitazone is used for the treatment of diabetes mellitus type 2. Pioglitazone selectively stimulates nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-gamma). It modulates the transcription of the insulin-sensitive genes involved in the control of glucose and lipid metabolism in the lipidic, muscular tissues and in the liver [14]. Pioglitazone acts as an agonist at peroxisome proliferator activated receptors (PPAR) in target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR-gamma receptors increases the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In this way, Pioglitazone both enhances tissue sensitivity to insulin and reduces hepatic gluconeogenesis. Thus, insulin resistance associated with type 2 diabetes mellitus is improved without an increase in insulin secretion by pancreatic β cells [15].

Construction of standard calibration curve of Pioglitazone

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 spectro-photometrically 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 spectro-photometrically at 280nm against pH 7.4 phosphate buffer as blank.

Preparation of Pioglitazone Transdermal Films

Matrix type transdermal patches containing Pioglitazone were prepared by solvent evaporation technique using different ratio of HPMC 15 and EudragitL100. The polymers were weighed in requisite ratios and allowed for swelling for about 6 hr in solvent mixture (1:1 ratio of methanol and chloroform) 15%v/W polyethylene glycol was incorporate as plasticizer. Then the drug solution was added to the polymeric solution, casted on to anumbra petriplate of surfaceareabout66.44 cm^2allowedforair-dryingovernightfollowedbyvacuumdrying for 8-10hr. The entire sheet was cutting to small patches with an area of 4.9 cm^2 i.e. with a diameter of 2.5 cm. 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 were incorporated. All formulations carried 15% v/w polyethylene glycol as plasticizer.

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

15% v/w polyethylene glycol – plasticizer, 5% v/w DMSO - penetration enhancer, Each patch 4.9 cm^2contains 3.67 mg of Pioglitazone

RESULTS

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

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.

Construction of standard graph of Pioglitazone

The standard graphs of Pioglitazone in methanol and pH 7.4 phosphate buffers were constructed. The standard graphs of Pioglitazone methanol and pH 7.4 buffers 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 pH 7.4 phosphate buffers has shown good linearity over a concentration range of 10-70µg/ml with R^2 of 0.9971. These graphs were utilized in estimation of Pioglitazone samples.

Development of Pioglitazone Transdermal Films

Films were formulated with HPMC E15 and EudragitL100. Many experiments were performed by varying the concentrations of polymer. The experiment was initiated by taking 0.2g 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.

Folding endurance number

The folding endurance numbers of HPMC E15 and Eudragit L100 containing patches has in the range of 435 to 566. 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.

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.

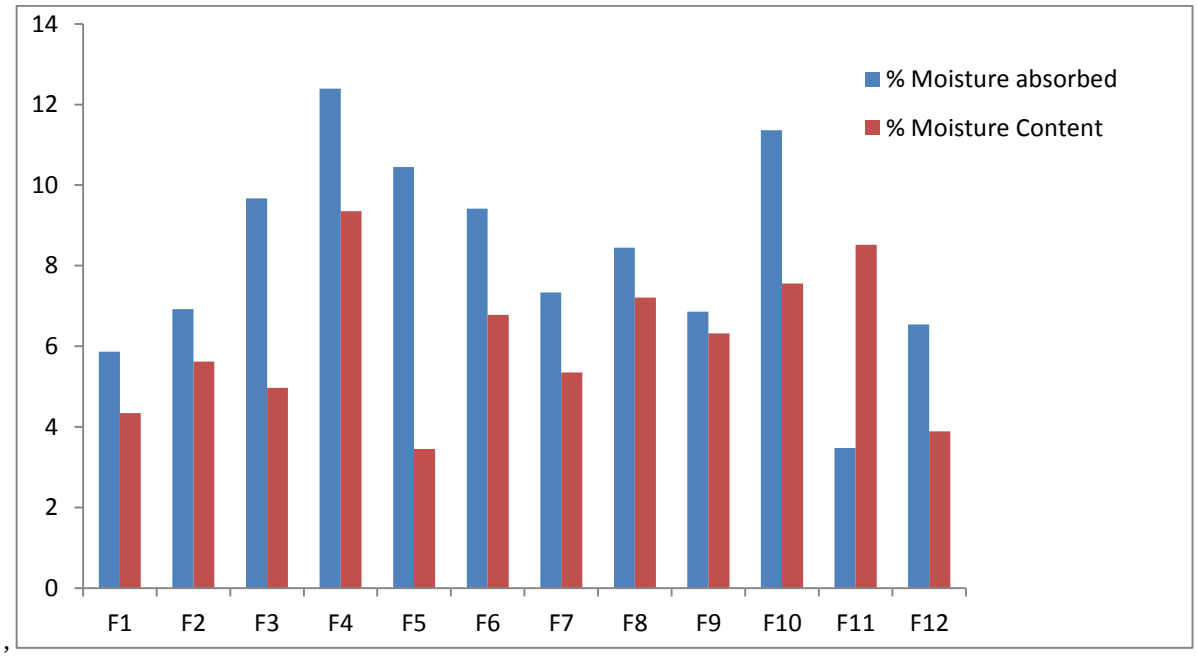
Table1 Weight variation, thickness and folding endurance of Pioglitazone transdermal patches

Formulation	Weight variation (mg)	Thickness (mm)	Folding endurance
F1	46.9±1.53	0.25±0.79	562.45±0.53
F2	33.76±0.97	0.2±1.27	435.12±1.38
F3	38.26±0.57	0.22±0.95	489.57±0.75
F4	42.41±1.26	0.23±0.83	550.77±0.93
F5	45.75±0.78	0.24±0.56	558.98±0.88
F6	32.37±0.49	0.19±1.54	432.48±0.64
F7	47.55±0.55	0.26±0.67	566.92±1.29
F8	35.45±1.12	0.205±0.98	454.1±1.02
F9	39.62±1.43	0.21±1.38	490.7±0.74
F10	40.78±0.89	0.24±1.26	558.57±0.62
F11	43.51±0.95	0.25±0.58	563.46±1.14
F12	33.25±0.67	0.215±0.63	470.79±1.09

Table 2 Drug content, % Moisture absorbed, %Moisture content of Pioglitazone transdermal patches

Formulation	Drug content (mg)	%Moisture absorbed	%Moisture Content
F1	3.35±0.96	10.87±1.58	9.34±0.96

F2	2.83±1.29	7.92±1.82	4.62±0.85
F3	3.05±0.84	9.67±0.95	5.97±1.17
F4	3.26±1.18	8.39±1.46	8.35 ±1.32
F5	3.29±1.04	10.45±0.93	8.45±1.95
F6	2.73±0.55	6.42±1.25	4.58±0.77
F7	3.42±1.37	11.44±1.03	9.35±0.94
F8	2.99±0.92	8.35±0.89	5.21±0.55
F9	3.16±0.75	8.86±0.64	6.32±0.79
F10	3.32±1.55	9.34±0.59	7.56±0.82
F11	3.38±1.27	10.48±1.19	9.12±0.93
F12	2.76±0.86	6.54±1.53	5.89±1.87



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Moisture absorbed and Moisture content of Pioglitazone transdermal patches

Table 3. Mechanical properties of optimized formulations

Formulation code	Tensile strength(kg/m^2)	Elongation at break (%mm^{-2})
F4	1.38±0.58	24.92±1.42
F9	0.76±0.34	43.18±1.03
F10	1.46±0.78	22.53±0.98

Table 4.Permeation of Pioglitazone from transdermal patches

Time (h)	Cumulative amount of drug permeated (µg/cm^2)			
	F1	F2	F3	F4
0	0	0	0	0
1	234.11±7.42	329.99±7.5	351.21±9.3	269.01±10.5
2	356.83±9.93	4599.48±10.4	490.67±10.56	412.14±7.5
3	457.2±9.92	610.3±12.35	590.87±8.79	583.53±9.3
4	621.16±10.32	779.14±7.95	711.98±13.25	751.24±8.9
5	801.86±7.58	966.31±10.32	845.2±9.5	940.62±7.5

6	966.53±11.38	1115.68±9.56	1042.28±8.7	1143.93±9.92
7	1171.3±17.56	1302.85±11.5	1217.33±8.5	1351.66±9.35
8	1367.93±18.56	1518.27±12.32	1417.72±7.5	1545.07±13.56
9	1513.6±12.79	1679.75±13.5	1626.91±10.5	1773.71±14.5
10	1686.8±8.97	1865.46±10.5	1831.33±7.32	2001.25±9.58
12	1909.33±12.1	2145.84±15.4	2243.28±10.2	2252.27±12.12
24	2357.3±19.46	2530.67±9.3	2754.54±9.1	3062.63±14.2
Flux J_{ss}	26.54± 1.05	29.4± 0.93	29.74 ±0.72	32.82 ±1.36

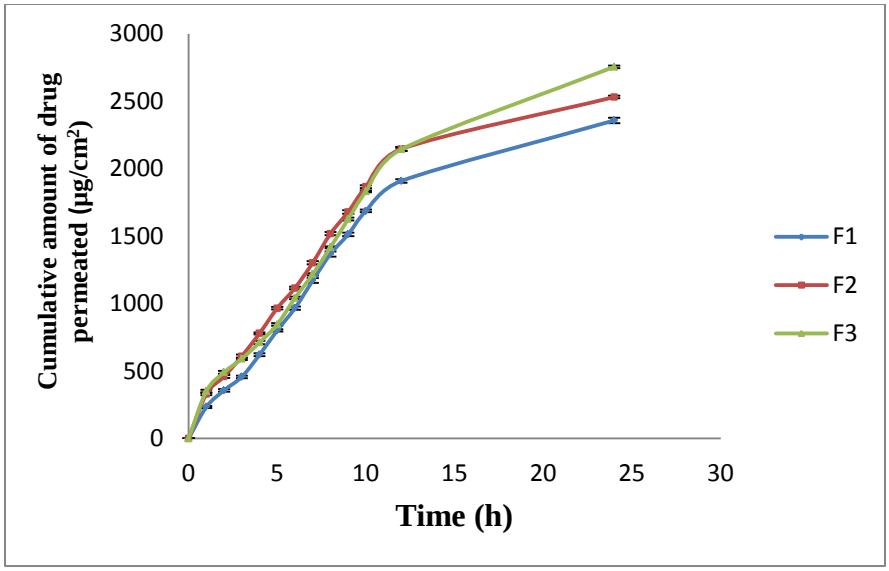

Fig 11. Permeation of Pioglitazone from transdermal patches

Table 11.Permeation of Pioglitazone from transdermal patches

Time (h)	Cumulative amount of drug permeated (µg/cm^2)			
	F5	**F6**	**F7**	**F8**
0	0	0	0	0
1	198.18±5.5	259.1±7.45	291.03±12.4	500.9±5.92
2	319.29±3.8	346.08±6.51	444.8±5.53	608.48±7.5
3	452.52±9.2	554.17±5.83	568.48±3.82	768.13±10.42
4	562.61±4.5	748.68±2.52	726.66±9.52	941.3±8.55
5	713.08±12.5	925.94±7.58	865.01±7.3	1058.06±9.31
6	886.67±10.5	1086.32±7.49	1080.08±7.84	1226.88±6.55
7	1080.08±3.6	1278.26±10.5	1272.38±5.3	1393.49±11.42
8	1258.81±4.7	1437.17±2.97	1487.45±2.68	1527.82±4.8
9	1451.85±8.5	1612.23±4.91	1690±4.72	1680.86±13.52
10	1655.17±2.5	1835±9.73	1816.65±8.35	1938.86±2.7
12	1905.83±3.9	2064.74±12.81	2063.6±6.7	2206.77±8.9
24	2269.35±6.7	2437.82±8.32	2597.64±10.5	2695.45±7.7
Flux J_{ss}	25.47± 0.85	28.32± 0.64	29.15± 1.54	31.04± 1.13

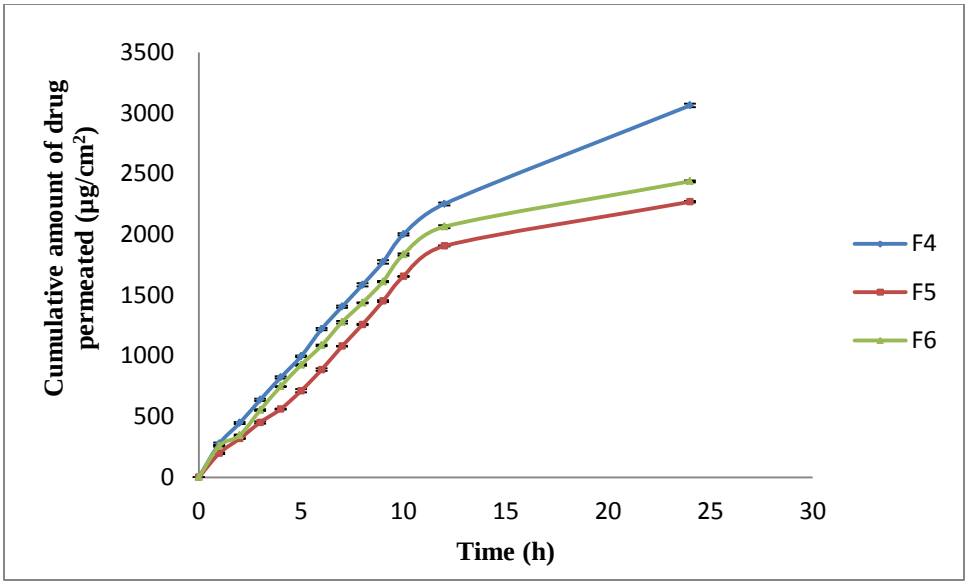

Fig 12. Permeation of Pioglitazone from transdermal patches

Table 12.Permeation of Pioglitazonefrom transdermal patches

Time (h)	Cumulative amount of drug permeated (µg/cm^2)			
	F9	**F10**	**F11**	**F12**
0	0	0	0	0
1	422.05±6.81	276.35±4.2	243.32±10.53	335.07±8.56
2	529.58±11.6	447.74±10.55	307.62±2.85	467.19±4.98
3	615.09±13.68	638.58±7.93	543.16±6.82	566.28±9.58
4	778.04±9.65	822.08±2.95	656.93±4.78	724.09±2.43
5	929.61±10.77	997.13±8.52	848.87±9.56	920.06±4.69
6	1142.47±4.37	1221±3.78	1054.39±13.87	1125.58±5.65
7	1362.67±5.68	1405.61±6.45	1294.4±12.54	1332.21±7.12
8	1567.09±6.45	1585.4±12.56	1518.27±9.55	1549.84±8.34
9	1776.28±9.52	1775.17±9.7	1696.64±10.23	1728.57±9.17
10	1986.57±10.55	1987.14±10.69	1861.79±8.94	1962.34±3.21
12	2284.94±7.45	2358.7±5.38	2021.06±6.52	2252.27±11.45
24	2963.54±3.24	3227.78±6.74	2411.93±9.25	2600.4±10.95
Flux J_{ss}	31.6± 0.56	33.4± 0.97	28.24± 1.28	30.2± 1.18

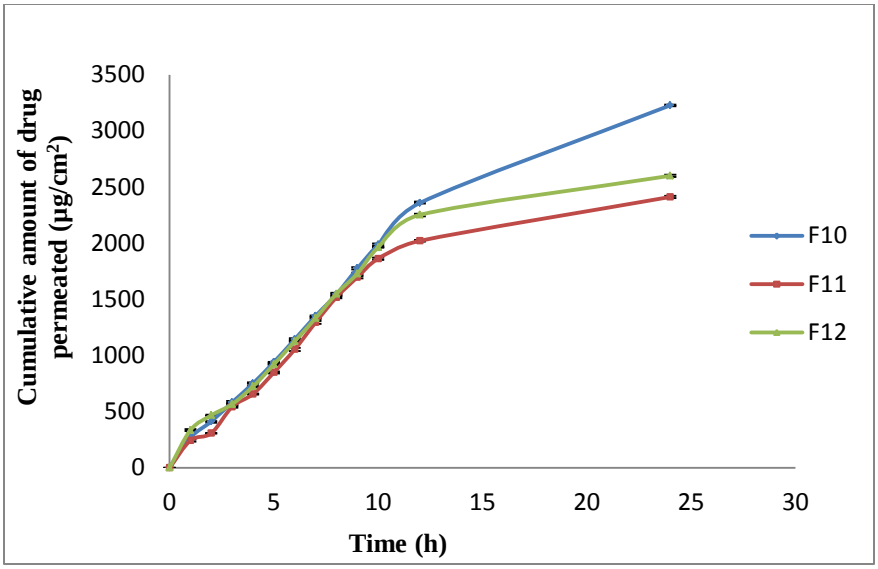

Fig 14. Permeation of Pioglitazone from transdermal patches

Conventional systems of medication that require multi dose therapy are having many problems. The controlled drug delivery is a newer approach to deliver drug into systemic circulation at a predetermined rate. Our system should duplicate continuous intravenous infusion, which not only by passes hepatic first pass elimination but also maintains a constant, prolonged and therapeutically effective drug level in the body. This is made possible by using intact skin as a port of drug administration to provide continuous delivery of drug into systemic circulation. The drug molecules are then transported to the target site, which could be relatively remote from the site of administration, to produce therapeutic action. Pioglitazone used in the treatment of Diabetes by decreasing blood sugar levels.

The aim of study is to prepare matrix type of Pioglitazone transdermal patch by using polymers HPMC E15 and Eudragit L 100 and to determine the drug release from these patches through Iontophoresis. Polymers HPMC are good thickness as well as matrix forming agents. Eudragit are also good film forming agents and best for the preparation of sustained release dosage forms. Matrix type transdermal patches containing Pioglitazone were prepared by solvent evaporation technique, using different ratios of combination of HPMC E15 and Eudragit L100 (F1to F6), and using DMSO as penetration enhancer (F7 to F12) in the above formulations, 15% polyethylene glycol was incorporated as plasticizer.

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.

The films prepared by general procedure were evaluated for the following properties such as weight variation, thickness, folding endurance, estimation of drug content, moisture absorption and moisture content determination, measurement of mechanical properties, *ex vivo* permeation studies, 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. The 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. In thickness variation test, 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 0.19±1.54 mm for F6 to 0.26±0.67 mm for F7. 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.

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±0.55mg 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. The moisture content in the patches was ranged from 4.58±0.77% for F6(HPMC E15&Eudragit L100) to 9.35±0.94% for formulation F7 with HPMC E15). The moisture absorption in the formulations is ranged from 6.42±1.25% for F6 (HPMC E15 & Eudragit L100) to 11.44±1.03 % for F7 (HPMC E15). 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.

Ex vivo permeation studies gives the results of *in vitro* Pioglitazone permeation through the rat skin from patches. The formulation F4 (HPMC E15 and Eudragit L100 ratio 10:2) exhibited the maximum (3062.63 µg) cumulative amount of drug permeation in 24 h, which was different from the formulation F1composed of HPMC E15 (2357.3µg). The formulation F10 (HPMC E15 and Eudragit L100, ratio 10:2) exhibited maximum (3227.78 µg) cumulative amount of drug permeation in 24 h, when DMSO was incorporated in the patch which was different from other formulations. The formulation F4i (HPMC E15 and Eudragit L100) i.e., through Iontophoresis showed maximum (3569.78 µg) cumulative permeation and a flux of 44.46 µg/cm^2/h compared with formulations F4 and F10. Formulations F1 and F7 composed of HPMC E15 showed less drug permeation as rigid films were obtained. 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 hypoglycemic 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 pharmacokinetic and Pharmacodynamic studies.

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