IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
June 2018 Vol.:12, Issue:3

Formulation and Evaluation of Pioglitazone Hydrochloride Buccoadhessive Patches

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Mona M. El Khatib[*1,2] , Walaa M. Mandour [3], Ibrahim A. Al Saraa [4]

1- *Department of pharmaceutics, college of pharmacy, Cairo University, Egypt*

2- *Department of pharmaceutics, college of pharmacy, king Saud University, Saudi Arabia*

3- *Department of pharmaceutics, college of pharmacy, king Saud University, Saudi Arabia*

4- *Department of pharmaceutics, college of pharmacy, king Saud University, Saudi Arabia*

Submission: 22 May 2018
Accepted: 29 May 2018
Published: 30 June 2018

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Pioglitazone, Hydroxypropylmethylcellulose, Eudragit, systemic delivery, Mucoadhesion, Buccal patches.

ABSTRACT

The aim of the study was to design and evaluate mucoadhesive buccal patches of pioglitazone for treatment of type 2 diabetes mellitus as the buccal region offers an attractive route of administration for systemic drug delivery. Buccal patches for systemic administration of pioglitazone in the oral cavity has been developed using hydroxypropylmethylcellulose, (HPMC), methylcellulose (MC), ethylcellulose (EC), and eudragit, either alone or as mixtures, by a solvent casting method. The physicochemical interactions between drug and polymers used were investigated by Fourier transform infrared (FTIR) Spectroscopy. According to FTIR the drug did not show any evidence of an interaction with the polymers used and was present in an unchanged state. The prepared patches were subjected to evaluation for their physical characteristics like weight variation, thickness, drug content uniformity, surface pH, folding endurance, tensile strength, mucoadhesion strength and were found very significant. *In-vitro* release studies were conducted for pioglitazone patches in phosphate buffer (pH, 6.8) solution using a USP dissolution tester. Patches exhibited drug release in the range of 46.6% to 93.2% in 210 min. When the release data were evaluated by a simple power equation ($Mt/M = kt^n$); it was observed that drug release from most of the formulated patches followed non-fickian release kinetics.

1. INTRODUCTION

While newer and more powerful drugs continue to be developed, increasing attention is being given to the methods by which these active substances can be administered (Kost and Langer, 2012). The sites of drug administration in the oral cavity include the floor of the mouth (sublingual), the inside of the cheeks (buccal) and the gums (gingival).

Delivery of drugs through the buccal mucosa has gained significant attention as an attractive alternative to the peroral route of drug administration because it overcomes many of the problems associated with the latter mode of administration. Problems such as poor oral bioavailability due to high first-pass metabolism and drug degradation in the harsh gastrointestinal (GI) environment can be circumvented by administering the drug via the buccal route. Moreover, the buccal route is easily accessible, has a good patient acceptance and compliance and can be used in patients who cannot swallow. The buccal route also offers a safer method of drug utilization since the drug absorption can be promptly terminated in cases of toxicity by removing the dosage from the buccal cavity. Therefore, several adhesive mucosal dosage forms were suggested for oral delivery, which included adhesive tablets, adhesive gels, adhesive films, adhesive patches, adhesive disks, and adhesive strips (Elkheshen et al., 2007). Buccal patches are highly flexible and thus much more readily tolerated by the patient than tablets. Patches also ensure more accurate dosing of the drug compared to gels and ointments.

Pioglitazone hydrochloride(Figure1) is an oral antidiabetic agent belonging to the class of thiazolidinediones, class of medications acts primarily by decreasing insulin resistance (Oo, 2007).

Pioglitazone hydrochloride is an odorless white crystalline powder. Concerning the chemical structure, pioglitazone hydrochloride is 5-(4-[2-(5-ethylpyridin-2- yl) ethoxy] benzyl) thiazolidine -2, 4-Dione, with a molecular weight of 392.90 daltons. It belongs to the Class II of the Biopharmaceutics Classification System and is practically insoluble in water, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile but soluble in organic solvents like methanol, dimethyl sulfoxide (DMSO), and dimethylformamide. It is available as a tablet for oral administration containing 15 mg, 30 mg, or 45 mg of pioglitazone (as the base). Pioglitazone hydrochloride is administered orally once daily without regard to meals. It is used alone (monotherapy) or in combination with a sulfonylurea

antidiabetic agent, metformin, or insulin as an adjunct to diet and exercise (Oo, 2007; Mohd et al., 2012).

Regarding pharmacokinetics of Pioglitazone, it is rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations (C_{max}) observed within two hours. Food slightly delays the time to peak concentration (t_{max}) but does not alter the extent of absorption. The mean absolute oral bioavailability of pioglitazone is 83%. Pioglitazone is extensively (97% to over 99%) bound to plasma proteins, primarily to albumin, and has a rather small apparent volume of distribution (0.63 l/kg) (Jaakkola, 2007). Pioglitazone has a short biological half-life of 3-6 hours and is eliminated rapidly (Devi G., 2012).

Common adverse effects of pioglitazone include weight gain, fluid retention and plasma volume expansion, which can produce mild dilutional anemia, peripheral edema and can lead to or exacerbate heart failure (Jaakkola, 2007).

2. MATERIALS AND METHODS:

2.1. MATERIALS:

Pioglitazone was purchased from Asseel Chemicals Trading Corp.(Riyadh. Saudi Arabia). Hydroxypropylmethylcellulose (Methocell E4M Premium®) and Ethylcellulose (Ethocell® Standard 20 Premium) were obtained from Colorcon® Ltd.,(Dartford Kent, England), Eudragit® RLPO was obtained from Rohm GmbH, (Germany), Propylene glycol was obtained from Winlab Co., (Maidenhead, Berkshire, England), Methylcellulose (Viscosity 17-25 cps) was obtained from Winlab Co. (Maidenhead, Berkshire, England), Tween® 80 was obtained from Avonchem ltd.,(United Kingdom) , methanol and acetonitrile (HPLC grade) were acquired from BDH Laboratory Supplies (BDH Chemicals, Poole, UK), dimethyl sulphoxide DMSO (USP grade) was obtained from Sharlau Company (Barcelona, Spain), Sodium Hydroxide Pellets were obtained from Merck® (Darmstadt, Germany). All chemicals and solvents used were commercially available products of analytical grade and used as received.

2.2. METHODS:

2.2.1. Preparation of pioglitazone buccal patches

Blank drug-free patches were initially prepared and those exhibiting appreciable organoleptic properties like continuity, physical appearance and non-stickness were selected for pioglitazone incorporation while patches with any imperfections, were excluded.

Patches were prepared by solvent casting method using different hydrophilic and hydrophobic polymers (Khairnar et al., 2009). Different concentrations of polymer solutions were mixed in specified ratios as shown in Table (1). For all the prepared patches, a drug solution was prepared, accurately weighed pioglitazone (1% w/v) was levigated with dimethyl-sulfoxide(DMSO) (2.5%), to that, PG (5%), was added. Simultaneously, the polymer-solvent system (polymer solution) was prepared then added to the solution system.The viscous formed solutions were casted into glass Petri dishes of 5.5 cm diameter (area=23.77 cm^2) and were allowed to dry overnight on a flat surface in an oven at 40±0.5^{0}C. The dried film was peeled off carefully, cut into patches of dimensions (1×3 cm) each containing 10 mg pioglitazone/patch, then stored in a desiccators over anhydrous calcium chloride at room temperature after warping in wax paper.

2.2.2. Drug and polymer compatibility studies

To investigate any possible interaction between the drug and the polymers under investigation, FT-IR spectrophotometer method was used (Kumar, 2011). The samples of pure drug, pure polymers and physical mixture of drug and polymers were prepared separately and performed by palletization technique in potassium bromide (KBr) using IR press. The IR peaks of pure pioglitazone were analyzed and were compared with the peaks obtained from FTIR spectra of solid mixtures.

2.2.3. Evaluation of patches

2.2.3.1. Uniformity of weight of the patches

Three patches (1x3cm) of each formulation were taken and weighed individually using an analytical balance (Kumar et al., 2011). The average weights were calculated and the results were analyzed for mean and standard deviation.

2.2.3.2. Thickness uniformity of the patches

Three patches of each formulation were taken and the patch thickness was measured using an electron digital caliper at three different places and the results were analyzed for mean and standard deviation (Kumar et al., 2011).

2.2.3.3. Surface pH

Three patches from each formulation were allowed to swell by keeping in contact with 5 mL of distilled water for 1 hour, in test tubes at room temperature (Satyabrata et al., 2010) .The surface pH was measured by means of a pH paper placed on the surface of the swollen patch. The mean of three readings was recorded (Bhavya and Keshav, 2011).

2.2.3.4. Folding endurance

The flexibility of patches can be measured quantitatively in terms of what is known as folding endurance. The folding endurance of three patches was determined manually by repeatedly folding one patch at the same place till it broke or folded up to 200 times, which is considered satisfactory to reveal good patches properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. The mean value of three observations and standard deviation were calculated (Kumar et al., 2010).

2.2.3.5. Swelling index

The patch (1x1 cm) was weighed and placed in a pre-weighed stainless steel wire basket sieve of approximately 800 μm mesh screen. The mesh containing the patch sample was then submerged into 15 ml of the phosphate buffer pH 6.8 contained in a small beaker. At definite time intervals, the stainless steel basket was removed, excess moisture removed by carefully wiping with absorbent tissue and reweighed (Koland et al., 2010) . Increase in weight of the patch was determined at each time interval. The degree of swelling was calculated from the average of three measurement using the following equation (Tirosh et al., 1997):

$$\% \text{ swelling index} = (Wt - W0)/Wt \times 100$$

Where Wt is the weight of the patch at time t and W0 is the weight of the patch at time 0.

2.2.3.6. Determination of actual drug content in the prepared patches

This parameter was determined by dissolving three medicated patches (1×3 cm) of each formulation, each patch was designed to contain 10 mg of pioglitazone, by homogenization in separate 100 ml volumetric flask, a mixture of 50 ml of methanol, 25 ml DCM, and 25 ml of ethanol were added and continuously stirred in a horizontal shaker at 37 ± 0.5 ^{0}C at shaking speed of 100 rpm for 24 hours.Then an aliquot was withdrawn and filtered through Millipore filter (0.45 µm). The solutions were diluted suitably and measured against the corresponding blank solution, at λ_{max} 269 nm using a UV spectrophotometer. The average of the three patches was taken as final reading. The results were analyzed for mean and standard deviation (Kumar et al., 2011). The amount of drug dissolved was calculated. Percent drug content was taken as:

% Drug content = Experimental drug content / Theoretical drug content × 100

2.2.3.7. Determination of the physicomechanical properties of the prepared patch

The mechanical properties of the patches were evaluated using Instron® universal testing instrument equipped with a one kilogram load cell. The patch in dimension (1× 3 cm) free from air bubbles or physical imperfections was held between two clamps positioned at a distance of 1 cm. During measurement, the patch was pulled by the top clamp at a rate of 100 mm/min; the force and elongation were measured when the patch was broken. Measurements were run in triplicate for each patch. The resulting profiles were analyzed using the software of the instrument.

Two mechanical properties, namely, tensile strength and percent elongation were computed for the evaluation of the patch. Tensile strength is the maximum stress applied to a point at which the patch specimen breaks and can be computed from the applied load at rupture as a mean of three measurements and cross-sectional area of the fractured patch as described from the following equation (Koland et al., 2010):

Tensile strength = Force at break (N)/ Cross-sectional area (mm^2)

Percent elongation at break can be obtained from the following equation (Peh and Wong, 1999) :

$$\% \text{ Elongation at break } (mm^{-2}) = \frac{\text{increase in length (mm)}}{\text{original length (mm)}} \times \frac{100}{\text{cross sectional area (mm2)}}$$

2.2.3.8. In-vitro adhesion test of the prepared patches

The mucoadhesive performance of the patches was evaluated using rabbit buccal mucosa. The rabbit model was chosen because rabbits were reported to have non-keratinized mucosal lining similar to human tissue (Shojaei, 1998; Elkheshen et al., 2007). Rabbit buccal tissues were surgically excised and trimmed evenly from each cheek pouch of freshly sacrificed rabbits according to ethical King Saud University protocol. It was then washed in phosphate buffer pH 6.8 and stored at -10^{0}C upon removal. It was thawed to room temperature before the study.

The rabbit buccal mucosa was cut to a certain area of 3 cm^2, after that it was glued with cyanoacrylate adhesive on the ground surface of a holder made of plexiglass. The patch was glued to another holder of the same size.

The surface of the mucosal membrane was first blotted with a filter paper and then moistened with 25 µl of phosphate buffer with pH 6.8.

The two holders with mucosal membrane and patch were put in contact with each other with uniform and constant pressure between fingers for 1 minute (preload time) to facilitate adhesion bonding. The tissue holder with buccal mucosa (upper holder) was allowed to hang on an iron stand with the help of an aluminum wire fastened with a hook provided on the back of the holder; a pre-weighed lightweight polypropylene bag was attached to the hook on a backside of the formulation holder with a piece of aluminum wire. After the preload time, water was added to the polypropylene bag through an intravenous infusion set at a constant rate of 2 drops per second until the patch detached from the tissue. The water collected in the bag was measured and expressed as weight (g) required for detachment (bioadhesive strength). The average of three experiments was calculated.

Figure (2) shows a schematic presentation of the experiment design. The apparatus was assembled in the laboratory and a modification of the apparatus was previously applied by Parodi *et al.* 1996 through Habib *et al.* 2010.

Force of adhesion and bond strength for each patch was calculated according to the following equations (Deshmane et al., 2009):

Force of adhesion (N) = bioadhesive strength × 9.81/1000

Bond strength (Nm^{-2}) = force of adhesion/disk surface area

2.2.3.9. Determination of ex-vivo mucoadhesion time

Ex-vivo mucoadhesion time was performed after the application of the patches on freshly cut rabbit buccal mucosa. The rabbit buccal mucosa was fixed on the internal side of a beaker with cyanoacrylate glue. Each prepared patch was cut to pieces of area 1 cm^2; one side of each patch was moistened with 50 µl of phosphate buffer pH 6.8, and then pasted to rabbit buccal mucosa by applying a light force with the fingertip for one minute. The beaker was filled with 250 ml of phosphate buffer pH 6.8 and kept at 37± 0.5 ^{0}C for 2 min. A 50- rpm stirring was applied into the beaker to simulate buccal cavity environment The behavior of each patch was monitored until complete detachment or dissolution occurred, the time was recorded as the mucoadhesion time. Each experiment was repeated three times and the mean value was calculated (Perioli et al., 2004).

2.2.3.10. *In-vitro* release study

Dissolution apparatus USP type II rotating paddle method was used to study drug release from buccal patches (Singh et al., 2011). The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8 (Bhavya and Keshav, 2011). The release was performed at 37 ± 0.5°C, with a rotation speed of 50 rpm. Sodium Lauryl Sulphate (SLS) (1%) was mixed in the buffer to enhance the solubility of pioglitazone in the phosphate buffer(Singh et al., 2009) and also to promote sink conditions in the medium(Phillips et al., 2012). Buccal patches with dimensions (1×3 cm), equivalent to 10 mg pioglitazone per patch were attached to a glass slide with instant adhesive (cyanoacrylate) from one side to provide unidirectional release. The glass slide was located at the bottom of the dissolution vessel so that the patch remained on the upper side of the slide. An aliquot of five ml samples was withdrawn at predetermined time intervals (15, 30,45,60,90,120,150 and 180 min). The samples were compensated with equal volume of fresh phosphate buffer pH 6.8 kept at the same temperature. The samples were filtered through 0.45µm Whatman filter paper and assayed by UV spectrophotometer at λ=269nm.

Release kinetics studies

The mechanism of release was determined by fitting the obtained *in-vitro* release data to various kinetic equations, these models were zero order, first order, and Higuchi models to assess the pattern of drug release and was confirmed with Korsmeyer-Peppas model.

3. RESULTS AND DISCUSSION:

As for the visual inspection, all the prepared polymeric patches were elegant in appearance, homogeneous, thin, flexible, possesses a smooth surface and no spot or stain was found on the patches.

3.1. FTIR. Studies of pioglitazone

FTIR Spectrum of pure pioglitazone (Figure 3) was compared with the FTIR spectrum of a physical mixture of pioglitazone with all the polymers used in the formulae. There was no appearance or disappearance of any characteristics peaks. This reveals that there is no chemical interaction between the drug and the polymers used in the patches. The presence of peaks at the expected range confirms that the materials taken for the study are genuine.

3.2. Weight variation test

The patches were found a uniform in the range of 46± 0.003 mg and 66± 0.007 mg as indicated by the low values of standard deviation (Table-2). The wide range may be due to different densities of polymers used.

3.3. Thickness uniformity of patches

All the patches had a uniform thickness within each formula. The average thickness was found to be in the range of 0.135± 0.007 mm to0.245± 0.049mm (Table-2).

3.4. Surface pH

As an acidic or alkaline pH may cause irritation to the buccal mucosa, an attempt was made to keep the surface pH close to salivary pH (5.5-7). The surface pH of the prepared patches was found to be in the range of 6.87± 0.003 to 6.98± 0.014, as shown in (Table-2). No significant difference was observed in the surface pH of different formulations ($P > 0.05$)

consequently; the surface pH for all the formulations was within the range of neutral pH which does not cause irritation and ultimately achieves patient compliance.

3.5. Folding endurance

All tested patches did not show any cracks even after folding for more than 200 times, hence it was taken as the endpoint, indicating the good flexibility of prepared patches.

3.6. Drug content

Actual pioglitazone content in the prepared patches was in the range of 44.44- 105.2% of the claimed content. This indicates the even and uniform distribution of the drug in the prepared matrix of the patches as well as the stability of pioglitazone in the procedure used for preparation (Table-2).

Physicochemical characteristics of the medicated patches

From the results of the tests for physical characterization conducted, it was observed that the weight was in the range of 46± 0.003 mg and 66± 0.007 mg and thickness in the range of 0.135± 0.007 mm to0.245± 0.049mm of all patch samples were uniform within each formulation. Pioglitazone patches were homogenous, clear and flexible. All patch formulations exhibited good folding endurance exceeding 200, indicating that they are tough and flexible. Also, the prepared formulations provided an acceptable pH range (6.87± 0.003 to 6.98± 0.014) that is compatible with normal pH of the buccal mucosa. The average percentage of drug content of various patches ranged from 8544.44% - 105.2% of the claimed content. This indicates the even and uniform distribution of the drug in the prepared matrix of the patches as well as the stability of pioglitazone in the procedure used for preparation (Table 2).

3.7. Swelling index

The swelling profiles of all formulations were shown in (Figure 4), no statistically significant difference was found among different formulations ($P > 0.05$). These profiles indicate that the maximum swelling takes place within 15 minutes in F-2 containing the higher portion of HPMC (1.5%) followed by F-4 (HPMC /MC) then F-1 (HPMC1%) and finally comes F-5> F-3 > F-6 respectively. It has been reported that the addition of hydrophilic polymer HPMC seems to increase the surface wettability and consequently swelling of the patches(Koland et

al., 2010). This finding describes the maximum swelling occurring in F-2 containing the highest amount of HPMC polymer followed by F-4 containing a combination of two hydrophilic polymers namely HPMC and MC. It was also observed that F-1 and F-5 showed approximately the same swelling index indicating that incorporating Tween 80® in the formula has no observed effect on the swelling. This may be due to the fact that, PG can absorb moisture from the environment because of its humectant ability resulting in an increase of patch moisture uptake (Rasool and Khan, 2010).

The least swelling indices were observed in those containing proportions of Eudragit and EC which are water-insoluble polymers and less hydrophilic and therefore subject to lesser swelling upon hydration (Koland et al., 2010). When the patches were placed in phosphate buffer pH 6.8 complete swelling followed by erosion was observed indicating that the drug release mechanism involves swelling of the polymer initially followed by drug release from the swollen matrix by diffusion, this agrees with the result found by (Vamshi Vishnu et al., 2007). The plateau seen in the swelling profiles may be due to that there was no further un-hydrated polymer to hydrate and expand or due to the protective gel coat that only allows a small quantity of water to diffuse into the inner core (Panigrahi et al., 2004).

3.8. Determination of the physicomechanical properties of the prepared patches

Table (3) depicts the physicomechanical properties of the prepared patches. It is observed from the results of the test that as the percentage of the mucoadhesive polymer, HPMC in the formulation F-2 (HPMC 1.5%) increased, the TS also increased, while EB slightly decreased when compared to F-1 (HPMC 1%), but still high enough to provide hard and rough patches. This result was in agreement with the result of(Yamsani et al., 2008) who have reported that TS increased with the increase in polymeric content but EB values decreased with the increase in polymer content.

3.9. *In- vitro* bioadhesion test of the prepared patches

The bioadhesion strength of all formulations was in the range of 45.75 ± 3.464 g to 20.6 ± 1.979 g as shown in Table (4) and (Figure 5). The highest bioadhesive strength and bond forming capacity with mucin were recorded for F-1 that contains 1% HPMC, this may be referred to that HPMC shows mucoadhesive interaction resulting from hydrogen bonding or other types of bonding made possible by the hydrophilic nature of the polymer (Kumar et al., 2010). A slight decrease in the bioadhesion strength was observed in formulations F-4

(MC/HPMC), and F-5 (Tween 80®), with no significant difference between these formulations in bioadhesion strength ($P > 0.05$).

For F-4 (MC/HPMC), although a non-significant decrease in bioadhesion strength was observed, but a significant decrease in bond forming capacity ($P < 0.05$) occurred; this may be due to the lesser chain flexibility of MC which reduces the chance of formation of an intimate polymer/mucosa contact required for good mucoadhesion (Aboofazeli, 2000). For F-3 (Eudragit/HPMC), the addition of Eudragit to HPMC polymer did not show any significant difference that is because Eudragit has no swelling properties, it only showed good film-forming property (Patel et al., 2009).

However, on increasing concentration of HPMC the bioadhesion strength as well as the bond forming capacity decreased as observed in F-2 (HPMC1.5%); this may be attributed to the high swelling of HPMC that produces a non-adhesive mucilage layer near the polymer/mucosa interfacial surface, this finding was supported by the result of the swelling as F-2 (HPMC1.5%) showed the highest swelling index.

Also, on increasing concentration of HPMC in formula F-2 (HPMC 1.5 %), the bioadhesion strength decreased, this may be attributed to as the concentration of the polymer increased, a high polymer entanglement and complexation occurs. This leads to reduced availability of free functional groups of polymer to a substrate and consequent slight decrease in bioadhesion so the drug release was retarded significantly when compared to F-1 (HPMC 1%) ($P < 0.05$). (Giradkar et al., 2010). The lowest bioadhesion strength with moderate bond forming capacity was observed for F-6 (EC/HPMC), this may be due to the hydrophobic nature of EC polymer which has no bioadhesive properties as reported by (Alanazi et al., 2007).

3.10. Determination of *ex-vivo* mucoadhesion time

The results of mucoadhesion time for the prepared patches, Figure (6), showed that there was a gradual increase from 45± 4.15 min for F-5(Tween80/HPMC), till 108± 3.03 min for F-3 (Eudragit/HPMC) with a significant difference in the adhesion time of the formulated patches ($P < 0.05$). Analyzing these results shows that incorporating Eudragit with HPMC in F-3 showed the longest duration of all formulae which is attributed to the behavior of Eudragit which, in addition to its role as film-forming polymer, possesses non-neglectable mucoadhesive properties that enhanced mucoadhesion (Shehata et al., 2011). When using

HPMC, mucoadhesion time always was increased, because the polymer although having high swelling, tends to retain its structure that, in turn, is better dissolved (Mishra et al., 2011) this appeared clearly as F-2 (HPMC 1.5 %) showed a long mucoadhesive time. It was also observed that the increase in water-soluble content promotes faster dissolution of the patch (Shehata et al., 2011). This can be observed with these formulations in descending order; F-4 (MC/HPMC)>F-6 (EC/HPMC) > F-1 (HPMC 1%)> F-5 (Tween80).

3.11. *In-vitro* release study

The drug release pattern was studied for all formulations for 210 minutes and the results are provided in Figure (7).

According to the results obtained, it was found that no lag time was observed as the patches were directly exposed to the dissolution medium, which offered a burst drug release during the first 15minutes (being more than 20 %). Drug release from hydrophilic matrices is dependent on factors like swelling and dissolution of the polymers, giving rise to the mass erosion of the system, concomitantly with dissolution and diffusion of the drug. Initially, the matrix thickness increases due to hydration and swelling of polymer then the matrix thickness decreases and finally disappear due to polymer dissolution as well as the dissolution of the drug. This phenomenon has been referred to as "swellable soluble matrix" (El-Samaligy et al., 2004).

The drug release rate was highest in F-4 (MC/HPMC) and followed by F-2 (HPMC 1.5%), as observed, the drug release rate appeared to increase with increasing amount of the hydrophilic polymers, (John et al., 2010). The increase in the rate of drug release could be explained by the ability of the hydrophilic polymers to absorb water, thereby promoting the dissolution, and hence the release, of the drug. (Patel et al., 2009).Incorporating hydrophobic polymers namely Eudragit and EC ,had an effect in significantly decreasing the release of the drug ($P < 0.05$) compared to F-4(MC/HPMC) , in F-3 (Eudragit/HPMC) the release was found to be less than F-1 and F-4 which could be attributed to the high hydrophobicity and cross-linking of Eudragit which retards the drug release from the patch (Babu et al., 2012). As EC was also a hydrophobic polymer, its incorporation in F-6 was expected to provide a controlled drug release , but it provided not so much difference when compared to F-1 (HPMC 1%), this may be attributed to the nature of the network within the patch which may

be loose with consequent ease of penetration of the dissolution medium and diffusion of the drug from the patch matrix (Attama et al., 2008).

Data of the *in-vitro* release were fitted to different equations and kinetic models. The kinetic models used were zero-order, first-order, Higuchi diffusion model and Peppas model. The values of the release exponent (*n*), a kinetic rate constant (k) and determination coefficient (R^2), are presented in Table (5). The best fit with the highest determination coefficients (R^2) was shown by Peppas release model followed by Higuchi model and then zero-order equation. This revealed that the release mechanism approximated more probably to Peppas equation which describes drug release from a polymeric system.

Noticing the results, it was found that F-1 exhibited a Higuchi model of release shown by the best R^2 value; this model of release resembles the fickian diffusion of a drug from a polymeric matrix. Also when the Korsmeyer peppas model was applied, in case of F-1, the (n) value was very small, the low values of n (< 0.5) indicated that the mechanism of drug release from all the formulae could be described as a quasi-Fickian diffusion mechanism. As for F-2, a first order release was observed with the best R^2 value of 0.987, with a non fickian diffusion pattern indicated from the peppas value of n=0.659. The results indicated that the release mechanism shifted from diffusion-controlled to an anomalous transport (non-Fickian diffusion) in which both diffusions of the drug from the matrix as well as erosion or dissolution of the matrix itself are governing the drug release from these formulations. For F-3, which also exhibited the best R^2 in the Higuchi model, the (n) value in peppas model equal to 0.498 indicated a fickian diffusion confirming the results obtained from the Higuchi diffusion model. In the case of F-4, the release mechanism was observed in the first order kinetics as well as Higuchi diffusion model; these findings were confirmed with the results of peppas model which indicated a non-fickian (analomus) mechanism of transport, indicating a coupling of diffusion and erosion mechanisms. F-5 and F-6 both showed a zero order release according to the best R^2 value of both. By applying the data in peppas equation, they both also showed a low (n) value suggesting a rather fickian release.

Regarding the release rate constant (k) which incorporating the structural and geometric characteristics of the release, its value becomes higher as the drug releases faster from the patches. The slowest release rate was obtained from F-2 (HPMC/1.5%) followed by F-4 (HPMC/MC). This decrease in the release constant increases the time needed to release a given quantity of drug, allowing a greater hydration and relaxation of the polymer matrix

before release. Thus, resulting in shifting the release mechanism toward relaxation- erosion; which may give some controlled drug release characteristics to the patch(Mehrgan and Mortazavi, 2010). This was in agreement with *n* value of F-2 (0.659) and F-4 (0.593) which indicated non-Fickian diffusion. On the other hand, the fastest release rate was obtained from F-1 (HPMC 1%), followed by F-6, F-5 and F-3 respectively.

4. CONCLUSION

Evaluation of pioglitazone buccoadhesive patches prepared by solvent casting technique using different polymers includes; Eudragit®, hydroxypropylmethylcellulose E4M, ethyl cellulose, and methyl cellulose, either alone or as mixtures, was carried out. The results revealed that all patches showed good morphological properties, swelling index and mechanical properties and uniform drug distribution. FTIR study of different pioglitazone patches prepared with different polymers showed no drug/polymer interaction in the patches. F-4 (HPMC/MC) showed a long residence time, promising controlled and complete drug release within 210 minutes, acceptable elasticity (12.104%mm-2), swelling index (86.23% in 15 minutes) and surface pH (6.5). In addition, this buccal patch is very tolerable and comfortable because it is non-irritant and may be preferred over adhesive tablets in terms of elasticity, flexibility and capability to protect the wounded or inflamed surfaces. The patch will also have advantages as it does not require water for intake and not to be professionally delivered so, it requires little or no patient compliance for success. The results indicated that the mucoadhesive buccal patches of pioglitazone may be a good choice to avoid the undesirable systemic side effects and can be proposed as a new therapeutic tool against diabetic disease. However, proven clinical efficiency remains the ultimate measure of success of any treatment regimen, hence; further studies using patient suffering from diabetes are required to confirm the effectiveness of the proposed buccoadhesive patch.

REFERENCES

1. Aboofazeli, S. a. M. R., 2000. Preparation and *in-vitro* assessment of various mucosa-adhesive films for buccal delivery. DARU Journal of Pharmaceutical Sciences. 8.
2. Alanazi, F. K., Abdel Rahman, A., Mahrous, G. M., Alsarra, I. A., 2007. Formulation and physicochemical characterization of buccoadhesive films containing ketorolac. Journal of drug delivery science and technology. 17**,** 183-192.
3. Attama, A., Akpa, P., Onugwu, L., Igwilo, G., 2008. A novel buccoadhesive delivery system of hydrochlorothiazide formulated with ethyl cellulose hydroxypropyl methylcellulose interpolymer complex. Sci Res Essay. 3**,** 343-347.
4. Babu, G. D., Sagar, K. C., Bhoot, M. R., Swaroop, A. P., Rao, N. V. B., 2012. DESIGN AND EVALUATION OF VALSARTAN TRANSDERMAL PATCHES. International Journal. 3**,** 461-464.

5. Bhavya, K., Keshav, K., 2011. PREPARATION AND INVITRO ASSESSMENT OF MUCOADHESIVE BUCCAL PATCHES OF LORAZEPAM. INTERNATIONAL JOURNAL OF PHARMACEUTICAL INNOVATIONS. 1.
6. . Devi G., R. C., 2012. Preclinical Pharmacokinetic Evaluation Of Pioglitazone Floating Tablets Formulated Employing Cross-Linked Starch-Urea. International Journal of Pharmacy and Pharmaceutical Sciences. 4, 104-106.
7. Deshmane, S. V., Channawar, M. A., Chandewar, A. V., Joshi, U. M., Biyani, K. R., 2009. Chitosan-based sustained release mucoadhesive buccal patches containing verapamil HCl. International Journal of Pharmacy and Pharmaceutical Sciences. 1**,** 216-229.
8. El-Samaligy, M. S., Yahia, S. A., Basalious, E. B., 2004. Formulation and evaluation of diclofenac sodium buccoadhesive discs. International Journal of Pharmaceutics. 286**,** 27-39.
9. Elkheshen, S., Ahmed, I., Aboul-Einien, M., Hassan, M., 2007. *In-vitro* And In-vivo Evaluation Of Controlled-Release Buccoadhesive Disks Of Timolol Maleate. Egyptian Journal of Biomedical Sciences. 23**,** 196-217.
10. Giradkar, K., Channawar, M., Kajale, A., Sridhar, E., Kamble, R., Bakde, B., Chandewar, A., 2010. Design development and *in-vitro* evaluation of bioadhesive dosage form for buccal route. International journal of pharma research & development. 2.
11. Habib, F., Azeem, M. A., Fetih, G., Safwat, M., 2010. MUCOADHESIVE BUCCAL PATCHES OF LORNOXICAM: I-DEVELOPMENT AND IN-VITRO CHARACTERIZATION.
12. Jaakkola, T., 2007. Pharmacokinetic interactions of pioglitazone.
13. John, A. S., Sathesh, B., Divakar, G., Jangid, M. K., Purohit, K. K., 2010. Development and evaluation of buccoadhesive drug delivery system for Atorvastatin calcium. Journal of Current Pharmaceutical Research. 1**,** 31-38.
14. Khairnar, A., Jain, P., Baviskar, D., Jain, D., 2009. Development of mucoadhesive buccal patch containing aceclofenac: *in-vitro* evaluations. International Journal of PharmTech Research. 1**,** 978-981.
15. Koland, M., Charyulu, R., Prabhu, P., 2010. Mucoadhesive films of Losartan Potassium for Buccal delivery: Design and Characterization. Indian Journal of Pharmaceutical Education & Research. 380**,** 315.
16. Kost, J., Langer, R., 2012. Responsive polymeric delivery systems. Advanced Drug Delivery Reviews.
17. Kumar, A., Phatarpekar, V., Pathak, N., Padhee, K., Garg, M., Sharma, N., 2011. Formulation development & evaluation of Carvedilol bioerodable buccal mucoadhesive patches. Int J. of Comprehensive pharmacy. 3**,** 1-5.
18. Kumar, M., Garg, G., Kumar, P., Kulkarni, G., Kumar, A., 2010. Design and *in-vitro* evaluation of mucoadhesive buccal films containing famotidine. Int J Pharma Pharmaceut Sci. 2**,** 86-90.
19. Kumar, V., Et Al., 2011. Formulation design, *in-vitro* evaluation and stability studies on mucoadhesive buccal films of anti-anginal calcium channel blocker. Journal of Applied Pharmaceutical Science. 01**,** 136-142.
20. Mehrgan, H., Mortazavi, S. A., 2010. The release behavior and kinetic evaluation of diltiazem HCl from various hydrophilic and plastic based matrices. Iranian Journal of Pharmaceutical Research. 4**,** 137-146.
21. Mohd, S., Kulkarni, A., Zaheer, Z., Dehghan, M., 2012. Spectroscopic Estimation of Pioglitazone Hydrochloride. International Journal of Pharmaceutical Frontier Research. 2**,** 87-94.
22. Oo, K. M. 2007. (Master thesis) *Bioequivalence Study of Pioglitazone Tablets in Thai Healthy Volunteers.* Mahidol University.
23. Panigrahi, L., Pattnaik, S., Ghosal, S. K., 2004. Design and characterization of mucoadhesive buccal patches of salbutamol sulfate. Acta Pol Pharm. 61**,** 351-360.
24. Patel, V. M., Prajapati, B. G., Patel, M. M., 2009. Design and *in-vitro* characterization of eudragit containing mucoadhesive buccal patches. International Journal of PharmTech Research. 1**,** 783-789.
25. Peh, K. K., Wong, C. F., 1999. Polymeric films as vehicle for buccal delivery: swelling, mechanical, and bioadhesive properties. J Pharm Pharm Sci. 2**,** 53-61.
26. Pence, H. E., Williams, A., 2010. ChemSpider: an online chemical information resource. Journal of Chemical Education. 87**,** 1123-1124.
27. Perioli, L., Ambrogi, V., Rubini, D., Giovagnoli, S., Ricci, M., Blasi, P., Rossi, C., 2004. Novel mucoadhesive buccal formulation containing metronidazole for the treatment of periodontal disease. Journal of Controlled Release. 95**,** 521-533.

28. Phillips, D. J., Pygall, S. R., Cooper, V. B., Mann, J. C., 2012. Overcoming sink limitations in dissolution testing: a review of traditional methods and the potential utility of biphasic systems. Journal of Pharmacy and Pharmacology. 64**,** 1549-1559.
29. Rasool, B. K. A., Khan, S., 2010. In-vitro evaluation of miconazole mucoadhesive buccal films. Int J Applied Pharm. 2**,** 23-26.
30. Satyabrata, B., Ellaiah, P., Choudhury, R., Murthy, K., Bibhutibhusan, P., Kumar, M. S., 2010. Design and evaluation of methotrexate buccal mucoadhesive patches. Int J Pharm Biomed Sci. 1**,** 31-36.
31. Shehata, S. M., Hassan, D., Maha, A., 2011. Formulation and Evaluation of Naproxen Mucoadhesive Buccal Patches for Local Effect.
32. Shojaei, A. H., 1998. Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Pharm Sci. 1**,** 15-30.
33. Singh, A., Patel, P., Bukka, R., Patel, J., 2011. PREPARATION AND EVALUATION OF BUCCAL FORMULATION FOR TRIAMCINOLONE. Int J Curr Pharm Res. 3**,** 74-80.
34. Singh, C., Jain, K., Kumar, C., Agarwal, K., 2009. Design and *in-vitro* evaluation of mucoadhesive microcapsules of pioglitazone. Journal of Young Pharmacists. 1**,** 195.
35. Tirosh, B., Baluom, M., Nassar, T., Friedman, M., Rubinstein, A., 1997. The effect of Eudragit RL-100 on the mechanical and mucoadhesion properties of polycarbophil dosage forms. Journal of Controlled Release. 45**,** 57-64.
36. Vamshi Vishnu, Y., Chandrasekhar, K., Ramesh, G., Madhusudan Rao, Y., 2007. Development of mucoadhesive patches for buccal administration of carvedilol. Current drug delivery. 4**,** 27-39.
37. Yamsani, M. R., Kishan, V., Yasmani, M., 2008. Development of Mucoadhesive Patches for Buccal Administration of Prochlorperazine: Evaluation of *In-vitro* Release and Mechanical Properties. Int. Phar Sci and Nanotech. 1**,** 64-70.

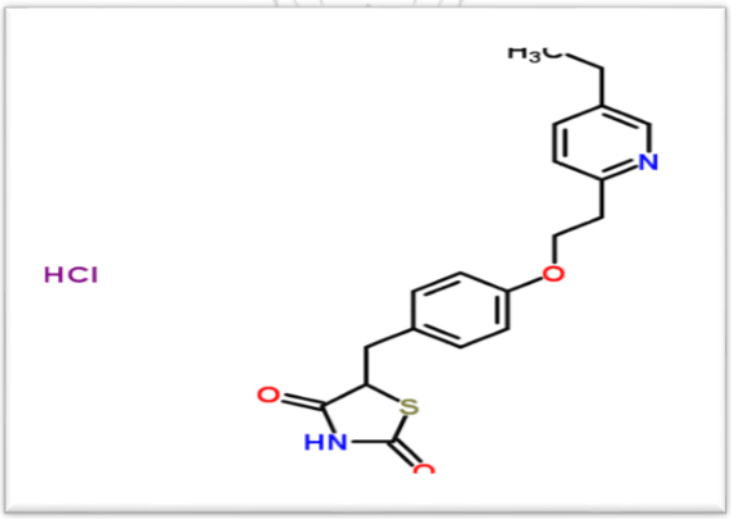


Figure (1): Chemical structure of pioglitazone HCl adopted from (Pence and Williams, 2010).

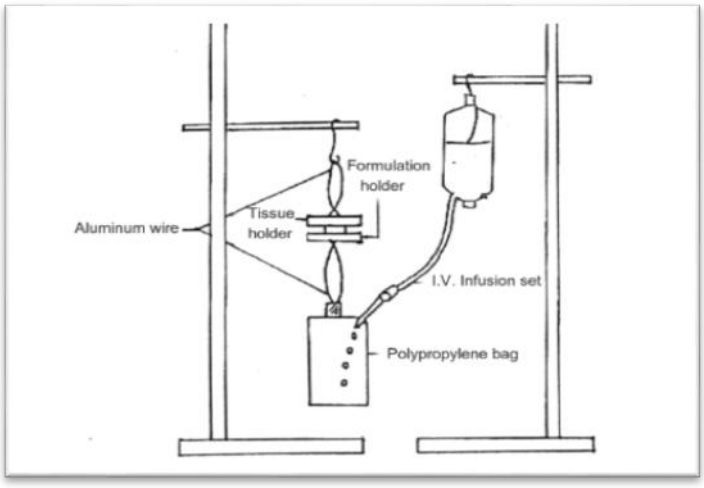
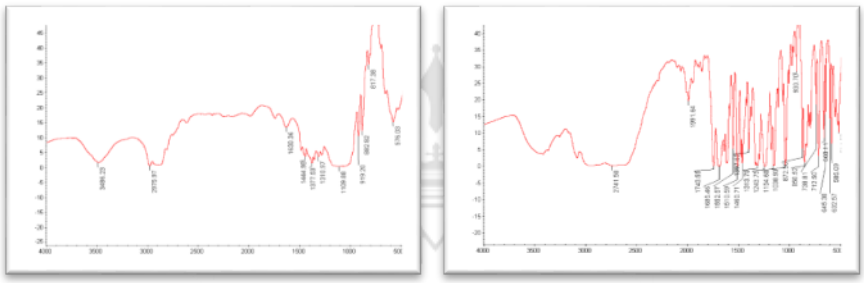
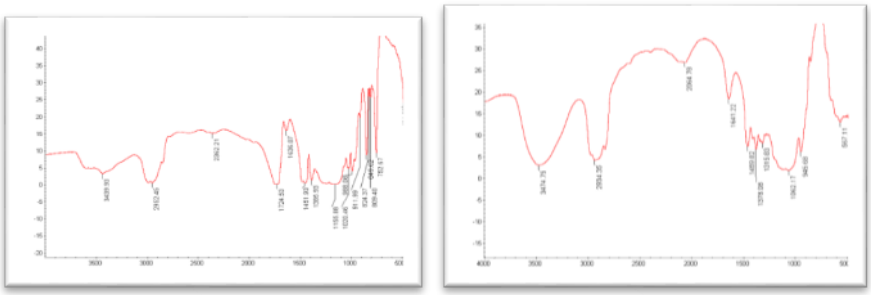


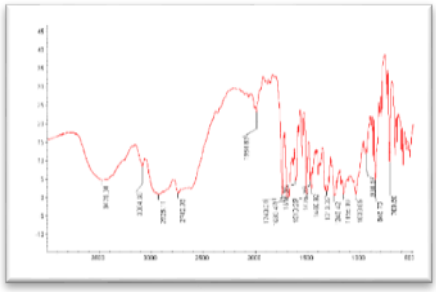
Figure (2): Modified apparatus for *in-vitro* bioadhesion test adopted from (Habib et al., 2010).



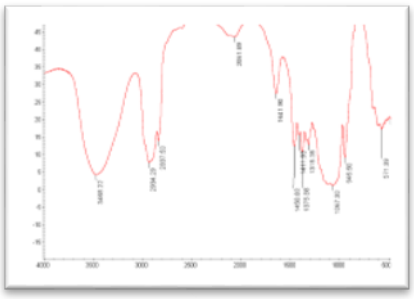
FTIR spectrum of Pioglitazone FTIR spectrum of EC



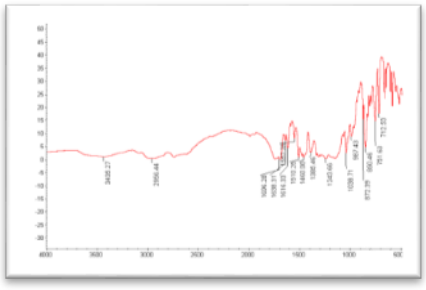
FTIR spectrum of Eudragit FTIR spectrum of HPMC



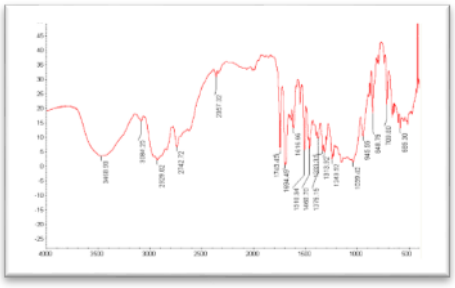
FTIR spectrum of MC



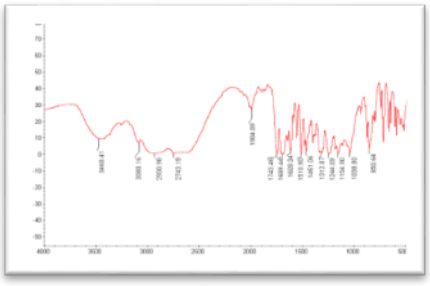
FTIR spectrum of Pioglitazone and HPMC (F1)



FTIR spectrum of Pioglitazone, HPMC and Eudragit®



FTIR spectrum of Pioglitazone, HPMC, and MC



FTIR spectrum of Pioglitazone, HPMC, and EC

Figure (3): Different FTIR spectra of drug, polymers, and formulae

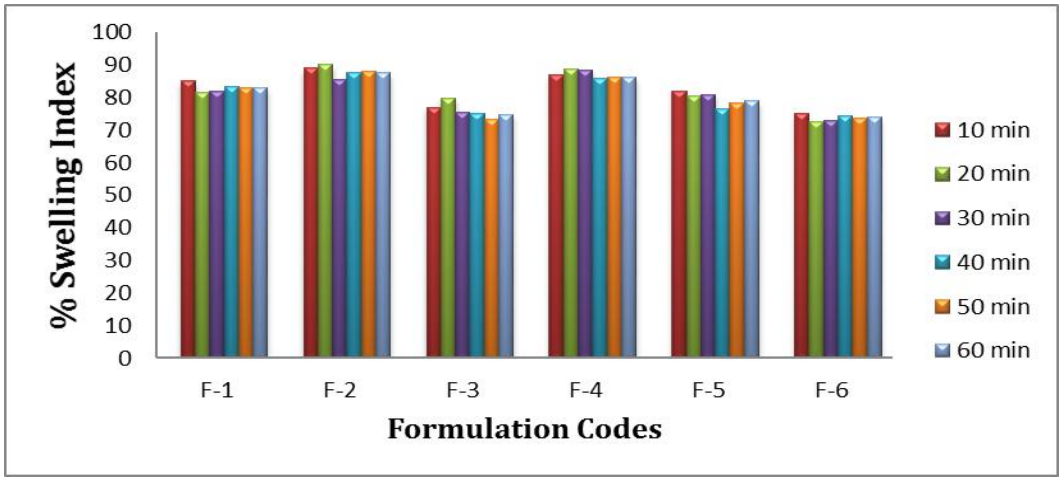


Figure (4): Swelling profiles of different pioglitazone patches in phosphate buffer pH 6.8

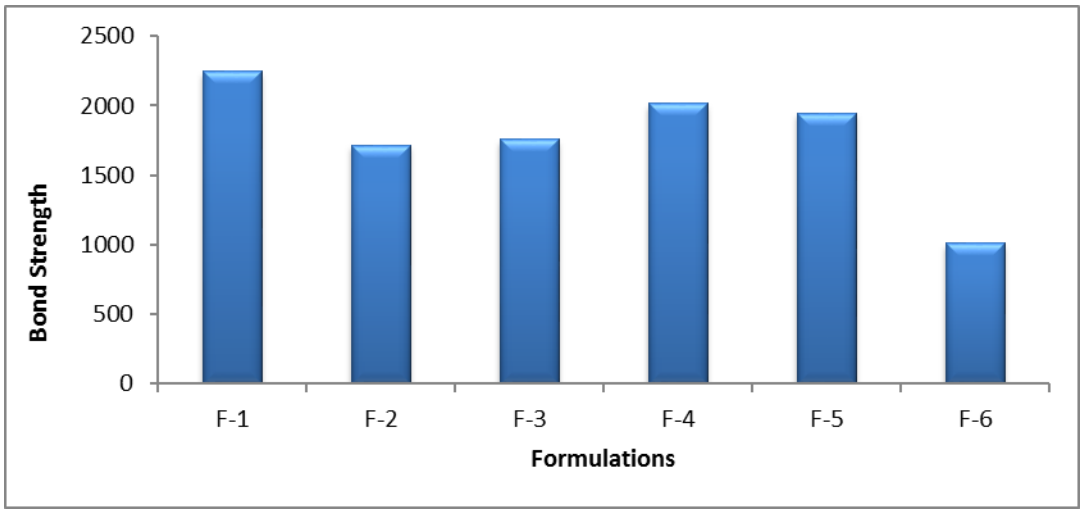


Figure (5): Bond strength of pioglitazone buccal patch

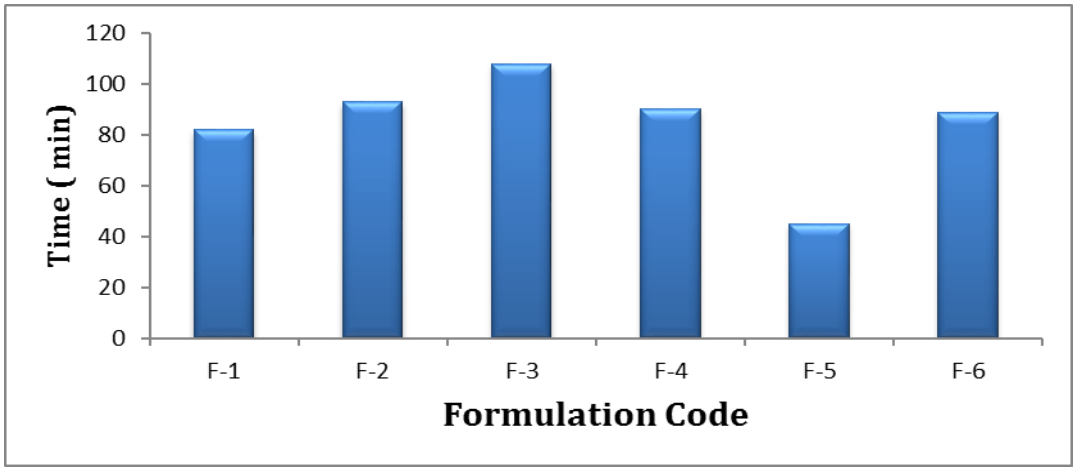


Figure (6): effect of different polymers on the *In-vitro* mucoadhesive(residence) time of different pioglitazone buccal patches

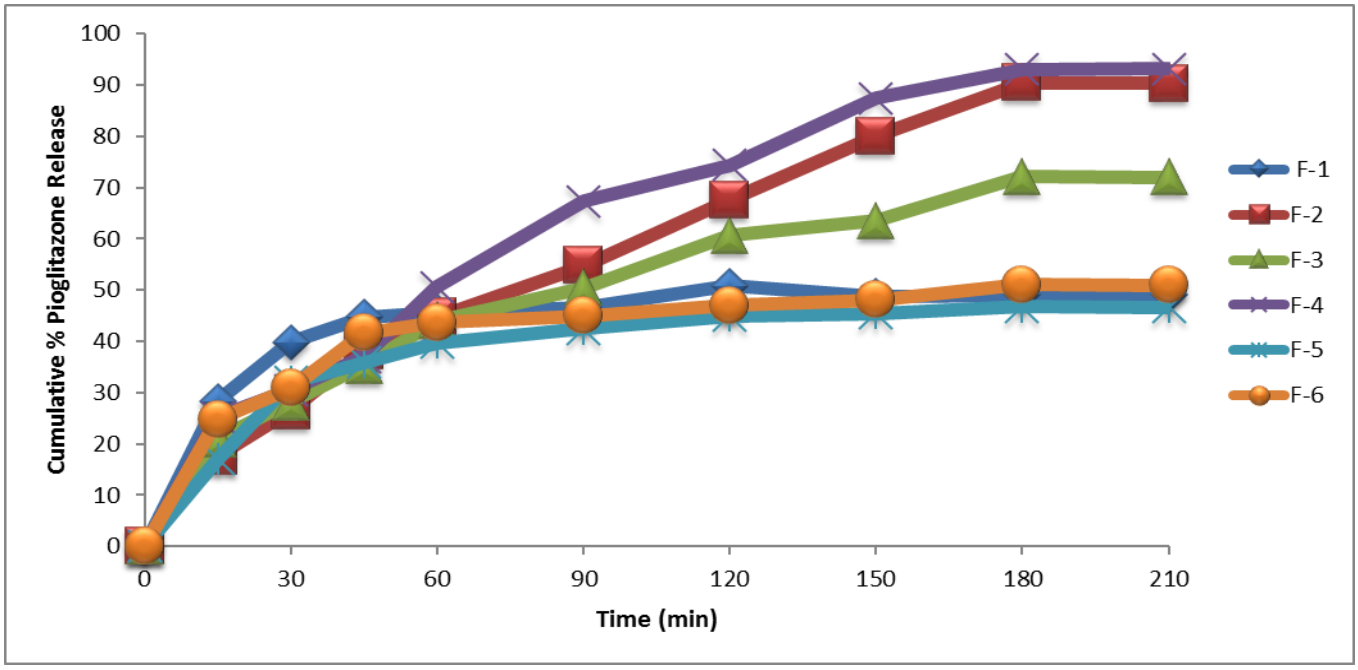


Figure (7): Release profiles of pioglitazone from different buccoadhesive patches in phosphate buffer pH 6.8

Table (1): Composition of different formulae of pioglitazone buccal patches

Formula	Pioglitazone HCL	HPMC E4M	Eudragit	Ethyl Cellulose	Methyl Cellulose	Propylene Glycol	Tween 80	Ethanol: DCM (1:1) up to	DMSO
F-1	1%	1%	-------	------	------	5%	------	100 ml	2.5%
F-2	1%	1.5%	------	------	------	5%	------	100 ml	2.5%
F-3	1%	1%	0.5%	------	------	5%	------	100 ml	2.5%
F-4	1%	1%	------	------	0.2%	5%	------	100 ml	2.5%
F-5	1%	1%	-------	-------	-------	4%	1%	100ml	2.5%
F-6	1%	1%	-------	0.5%	-------	5%	-------	100 ml	2.5%

Table (2): Physical characteristics of the formulated pioglitazone buccal patches*

Formulation code	Weight Variation (mg)	Thickness (mm)	Surface pH	Folding Endurance (times)	Average % Drug content
F-1	66± 0.007	0.15± 0.014	6.92± 0.004	>200	77.64± 0.039
F-2	64± 0.0037	0.14± 0.003	6.91± 0.007	>200	96.93± 0.109
F-3	50± 0.007	0.245± 0.049	6.87± 0.003	>200	78.89± 0.033
F-4	63± 0.005	0.164± 0.014	6.89± 0.007	>200	95± 0.061
F-5	46± 0.003	0.173± 0.004	6.88± 0.042	>200	44.44± 0.002
F-6	48± 0.01	0.135± 0.007	6.98± 0.014	>200	105.2± 0.088

*All observations represent the mean value ± SD (n=3)

Table (3): Mechanical properties of the formulated pioglitazone buccal patches

Formulation code	Tensile Strength (Mpa)	% Elongation at Break (mm $^{-2}$)
F-1	10.314± 0.002	18.251± 0.035
F-2	12.621± 0.028	16.851± 0.384
F-3	8.928± 0.131	12.853± 0.628
F-4	8.632± 0.023	12.104± 0.642
F-5	9.968± 0.015	17.887± 0.723
F-6	8.261± 0.152	15.462± 0.172

Table (4): Bioadhesion parameters of different pioglitazone buccal patches

Formulation Code	Bioadhesive Strength (g)	Force of Adhesion (N)	Bond Strength (Nm^{-2})
F-1	45.75 ± 3.464	0.4488075	2244.0375
F-2	20.6± 1.979	0.3514923	1757.4615
F-3	35.83 ± 0.791	0.3514923	1757.4615
F-4	39.65 ± 0.494	0.3889665	1944.8325
F-5	41.1 ± 2.687	0.403191	2015.955
F-6	34.95 ± 1.343	0.3428595	1714.2975

Table (5): the kinetic parameters of pioglitazone release data according to different kinetic models

Formulation code	Zero- Order		First- Order		Higuchi		Peppas		
	R^2	K	R^2	K	R^2	K	R^2	K	n
F-1	0.531	0.391	0.488	0.007	0.612	4.685	0.966	21.24	0.173
F-2	0.914	0.556	0.987	0.01	0.971	6.182	0.998	2.932	0.659
F-3	0.735	0.472	0.939	0.008	0.996	5.36	0.996	5.422	0.498
F-4	0.853	0.604	0.982	0.012	0.981	6.776	0.991	4.379	0.593
F-5	0.886	0.352	0.448	0.005	0.834	4.155	0.953	11.12	0.288
F-6	0.806	0.378	0.358	0.006	0.787	4.485	0.971	14.42	0.248